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# Potential Protecive Effect of Renin-Angiotensin-Aldosterone System Inhibitors in a Racially Diverse Sample, Hospitalized with Covid-19.

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**Abstract.**

**Objective:** To describe the clinical outcomes of Covid-19 in a raciall diverse sample from the US Southeast and examine the association of renin-angiotensin-aldosterone system (RAAS) inhibitor use with Covid-19 outcome.

**Design, Setting, Participants:** This study is a retrospective cohort of 1,024 patients with reverse-transcriptase–polymerase-chain-reaction-confirmed Covid-19 infection, admitted to a 1,242-bed teaching hospital in Alabama. Data on RAAS inhibitors use, demographics and comorbidities were extracted from hospital medical records.

**Primary Outcome**s: in-hospital mortality, a need of intensive care (ICU), respiratory failure, defined as invasive mechanical ventilation (iMV), and 90-day same-hospital readmissions.

**Results:** Among 1024 patients (mean [SD] age, 57 [18.8] years), 532 [52.0%] were African Americans, 514 [50.2%] male, 493 [48.1%] had hypertension,356 [35.6%] were taking RAAS inhibitors. During index hospitalization (median length of stay of 7 (interquartile range [4-15]) days) 137(13.4%) patients died; 170(19.2%) of survivors were re-admitted. RAAS inhibitor use was associated with lower in-hospital mortality (adjusted hazard ratio, 95%CI [0.56, (0.36-0.88), *P*=0.01) and no effect modification by race was observed (*P* for interaction = 0.81). Among patients with hypertension, baseline RAAS use was associated with reduced risk of iMV, adjusted odds ratio, 95% CI [aOR=0.58, 95%CI (0.36-0.95), *P*=0.03]. Patients with heart failure were twice as likely to die from Covid-19, compared to patients without heart failure.

**Conclusions:** Among racially diverse patients, hospitalized with Covid-19, pre-hospitalization use of RAAS inhibitors was associated with 40% reduction in mortality irrespective of race.

**Article summary.**

**Strength and limitations.**

- This study background was based on multiple questions on RAAS safety, raised by the community of the primary care physicians and patients in the beginning of the COVID-19 pandemic.
- Among racially diverse patients, hospitalized with Covid-19, pre-hospitalization use of RAAS inhibitors was associated with 40% reduction in mortality.
- Pre-hospitalization RAAS use did not increase the risk of admission to intensive care or same hospital readmissions.

**Introduction.**

The United States has experienced an unprecedented public health crisis with the Covid-19 pandemic.[1] Persons with cardiovascular and metabolic disease are at increased risk for mortality and morbidity from Covid-19[2-5]. Cardiovascular disease and diabetes mellitus are highly prevalent among US adults, with 45% of adults having HTN, 13% - diabetes mellitus, 6.7% - coronary artery disease, and 2.4% - heart failure[6]. These same chronic conditions disproportionally affect adults in the Southeast compared to other parts of the US[6]. Patients with hypertension, heart failure, diabetes, and chronic kidney disease are often prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors, i.e., angiotensin converting enzyme inhibitors (ACEi) or aldosterone receptor blockers (ARBs). In animal studies, performed prior to the emergence of Covid-19, ACEi were found to increase the expression of ACE2 receptors.[7] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to ACE2 receptors in lungs[8], leading to concerns about potential risks of utilizing RAAS inhibitors in the setting of Covid-19. While subsequent studies have demonstrated the safety of RAAS inhibitor use among persons with Covid-19 and indication for RAAS use[9-11], the association of RAAS use with hospital readmission after the index Covid-19 admission is not well described.

Most of reports[12] describing the associations of pre-existing use of RAAS inhibitors with COVID-19 outcomes, were obtained in White or Asian, not African American populations. Compared to Whites, African Americans have high incidence of RAAS inhibitor adverse effects[13]. Disprortinaly affected by muttiple health disparities, African Americans have also been shown to have an increased risk of severe COVID-19, requiring hospitalization[14]. Persons of African decent were at higher risk of contracting COVID-19 in the largest to date cohort study of the Covid-19 susceptibility in England[15].

To better understand the association of baseline RAAS inhibitor use with outcomes of Covid-19 hospitalization, we assembled an observational retrospective cohort of racially diverse hospitalizred patients with laboratory-confirmed Covid-19 in Alabama. We examined whether baseline RAAS inhibitor use was associated with Covid-19 health outcomes, including 1) in-hospital mortality, 2) need for Intensive Care Unit

(ICU) admission 3) acute respiratory failure requiring intubation and mechanical ventilation (iMV), and 4) same-hospital readmission for any cause among survivors of the Covid-19 index hospitalization. We assessed whether the association between RAAS inhibitor use and mortality differed by race.

**Methods.**

**Study participants and procedures.**

This observational retrospective cohort study included 1024 adult (age 18 and above) patients hospitalized with confirmed Covid-19 between March 1 and September 16, 2020 at the University of Alabama at Birmingham (UAB) teaching hospital in Birmingham, Alabama. Covid-19 cases were confirmed by reverse-transcriptase polymerase chain-reaction testing (rt-PCR). We electronically extracted patient data from our institution's Electronic Health Record (EHR; Cerner) data warehouse (i2B2) supplemented by manual chart review. Data were prepared for analyses by the COVID Core data Extraction/Transformation team using Oracle SQL developer (v.11.2). For each of the patients with lab-confirmed Covid-19, encounter data for the index admission were obtained, including admission date, date of the earlist positive rt-PCR for Covid-19 and death or discharge date. Additionally, the admission/discharge dates for all subsequent outpatient and inpatient encounters were extracted. Dates of death after the index hospitalization were also electronically extracted. For each of the hospital readmissions (n=172) a manual chart review was conducted to confirm admission/discharge dates. For each of the deaths (n=16) that occurred after index hospitalization we conducted manual chart review for confirmation. From the initial sample of 1029 patients, we excluded 5 patients with missing index admission dates or missing dates of birth. The study procedures were approved by the UAB Institutional Review Board.

**Patient and public Involvement.**

No patient involved.

**Outcomes and main exposure.**

Study outcomes included in-hospital Covid-19-related mortality, need for the ICU admission, respiratory failure defined by a need for invasive mechanical ventilation, and same-hospital readmission for any cause after

the index hospitalization. First cases of the Covid-19 were detected in Birmingham after March 1, 2020. The cases were very slowly increasing over the spring of 2020, with a sharp surge 10-14 days after July 4, 2020. After the initial surge, Covid-19 cases declined slightly in August 2020, but then started to rise constantly, achieving an unprecented spike in December-January 2021 (data not included in this report). The UAB ICU neared bur did not exceed the capacity. During the first surge of Covid-19 cases in July 2020, UAB Hospital has implemented a delayed intubation stategy, favoring treating Covid-19 respiratory failure with supplemental oxygen, delivered via high flow nasal canula. Therefore, all analyses of respiratory failure were adjusted for the time of the index admission for Covid-19 (before vs. after July 15, 2020).

Data on RAAS inhibitor included the use of ACEi and ARBs prior to the index Covid-19 hospitalization, and were derived from the index admission medication reconciliation data in the EHR. If patients were taking a combination medicine that included an ACEi or ARB as one of the components, they were classified as having been prescribed ACEi/ARB in the analysis.

**Covariates.**

Covariates were selected on the basis of the risk factors for severe Covid-19 infection identified by the Centers for Disease Control and Prevention and previous reports on Covid-19 morbidity and mortality [16-19]. Patient socio-demographic characteristics included age at the index admission (calculated, using birth and admission dates) and self-reported race, sex, marital status, and cigarette smoking status. We created age categories as follows: 18-40, 41-64, 65-74, and 75 years and older. Body mass index (BMI) was calculated using height and weight obtained most recenty prior to the index Covid-19 admission. BMI categories included: “underweight” is less than 18.5 kg/m$^2$, “normal weight” 18.5-24.9 kg/m$^2$, “overweight” 25-29.9 kg/m$^2$ and “obese” 30 kg/m$^2$, and above. We obtained data on comorbidities, including hypertension, coronary artery disease, diabetes, chronic obstructive pulmonary disease (COPD), heart failure, chronic kidney disease, HIV, sickle cell disease, and history of solid organ transplant using corresponding ICD-10 codes.

**Statistical Analysis.**

Patients with Covid-19 who were prescribed RAAS agents at baseline were compared to those who were not prescribed RAAS, using two-sided t-tests for continuous variables and Chi-square tests for categorical variables. We examined the association of RAAS inhibitors use with the study outcomes in three different samples: 1) overall sample, 2) patients with any indication for RAAS use, such as hypertension, diabetes, chronic kidney disease, coronary artery disease, and heart failure and 3) patients with hypertension. Outcomes were assessed with unadjusted and multivariable models. To examine the association of in-hospital mortality from Covid-19 with baseline RAAS inhibitor use we constructed Cox proportional hazards regression models adjusted for age, sex, race, marital status, smoking, BMI, and medical conditions. We created an interaction term between RAAS use and race to test for effect modification by race in the fully adjusted models of Covid-19 in-hospital mortality. The need for ICU and the presence of respiratory failure were examined separately in logistic regression models with adjustment for the same patient characteristics and for the time of admission (before vs. after July 15, 2020).

We examined the charts of the survivors of the index Covid-19 admission post-discharge for a same-hospital readmission for any cause using medical records. The EHR data were abstracted for any subsequent in-hospital and outpatient encounter after the index hospitalization and UAB hospital readmission dates were extracted. The time to reamission was calculated using index discharge data and readmission date. To examine the association between baseline RAAS use and readmissions we used the Fine and Gray Model to account for competing risk of death in the post-discharge period that was adjusted for the same patient characteristics. The proportionality assumption was tested and satisfied in the Cox proportion hazards models. All statistical analyses were performed in SAS software (SAS Institute, Cary, NC) version 9.4,

**Results.**

Among 1024 patients, admitted to UAB hospital with Covid-19 (mean [SD] age, 57 [18.8] years), 532 [52%] were African American, 514 [50 %] were male, 493 [48 %] had hypertension, 323 [32 %] had heart failure, 487 [48 %] were obese, 210 [20.5%] had diabetes and 98 [11 %] were current smokers (Table 1). There

were 356 [36%] patients taking RAAS inhibitors at baseline. Patients with baseline RAAS use were older, more likely to be African American, and had more comorbidities.

The median length of stay (LOS) for the index Covid-19 hospitalization was 7 days, [interquartile range (IQR) 4-15 days]. Maxiumun LOS was 175 days. Sixty percent of included Covid-19 cases were admitted after the initial surge in Birmingham, between July 15 and September 16, 2020. During the index hospitalization, 137 (13.4%) patients died. Additionally, 16 (1.8%) patients died from any cause post-discharge, either during a hospital readmission or out of the hospital. Cumulative all-cause mortality included 153 (14.9%) deaths. At the time of the cohort assembly on September 16, 2020, 23 patients remained in the hospital. During the index hospitalization 466 (45.5%) patients required ICU care, and 276 (27%) persons required iMV. The proprortion of patients who were intubated was higher in the early period, before July 15, compared to the period of after July 15,2020, when placing the patient with respiratory failure on high flow nasal canalula became a preferred treatment strategy: 201 [32.4%] vs. 75 [ 18.6], *P* <.001.

**In-hospital Covid-19 mortality and RAAS use.**

The median time to death was 13 days [IQR 6-20 days]. In the overall study sample, baseline RAAS inhibitor use was significantly associated with reduced risk of in-hospital mortality (adjusted hazard ratio [aHR] 0.56, 95% confidence interval [95%CI] 0.36-0.88], *P*=0.01, after adjustment for all covariates) (Figure 1). A similar protective effect of RAAS inhibitor use on mortality was observed among patients with any indication for RAAS inhibitor use (aHR [95%CI] for RAAS inhibitor use 0.59, 95%CI 0.37-0.94, *P*=0.03) and among patients with hypertension (aHR for RAAS use 0.54, 95%CI 0.33-0.90, *P*=0.02). We did not observe effect modification by race in the overall sample; the RAAS inhibitor use*race interaction term had associated *P*= 0.81. Compared to Whites, African American race was not associated with in-hospital mortality from Covid-19 in the adjusted model (aHR 0.88, 95% CI 0.60-1.29, *P* for trend 0.55) (Table 2).

Other factors associated with increased cumulative mortality in our sample included age 65-74 years (aHR 3.67 [95%CI 1.85-7.31]), age 75 years and older (aHR 4.89 [95%CI 2.36-10.14]), obesity (aHR 2.10 [95%CI 1.34-3.29]), and pre-existing heart failure (aHR 1.88 [95%CI 1.20-2.94]) (Table 2).

**Covid-19 in-hospital events and RAAS inhibitor use.**

RAAS inhibitor use was not associated with the need for ICU in all analyses (Figure 2.) In the overall patient sample, RAAS use was not associated with iMV, aOR 0.71[95%CI 0.48-1.06] (Figure 3). In contrast, among patients with hypertension, baseline RAAS inhibitor use was significantly associated with reduced odds of iMV after adjustment for covariates (aOR 0.58 [95%CI 0.36-0.95], *P*=.03). African Americans, admitted with Covid-19, were more likely to have respiratory failure, requiring iMV: aOR 1.58 [95%CI 1.01-2.31], *P*=.02. Another factors, associated with the increased risk of iMV for the Covid-19-related respiratory failure, included current cigarette smoking (aOR 1.80 [95%CI 1.08-3.02], *P*=.03), pre-existing heart failure (aOR 2.32 [95%CI 1.45-3.71], *P* <.001) and being admitted to UAB before July 15, 2020 (aOR 1.97 [95%CI 1.39-2.79], *P* <.0010.

**Same-hospital 90-day readmissions among Covid-19 survivors.**

Over a median follow up of 51 [IQR 28-82] days, 170 (19.2%) of 887 discharged patients were readmitted to the same hospital for any cause (Table 1). Since the index discharge, among those who were re-hospitalized, the median time to readmission was 10 days [IQR 4-29 days]. The proportion of persons with same-hospital readmission among those with baseline RAAS inhibitor use was 23.5%, compared to 16.7% among those who were not prescribed RAAS inhibitors *(P*=0.01) (Table 1). In the fully adjusted Cox proportional models, accounting for death as a competing risk, baseline RAAS agent use was not associated with readmissions (Table 3). Compared to White patients, patients of the Hispanic/Latino/Asian or other race/ethnicity were less likely to be readmitted (aHR 0.42, 95% CI 0.20-0.90). African-American race was not statistically significantly associated with hospital readmission (aHR 1.11, 95% CI 0.78-1.60). Among the chronic medical conditions only diabetes was significantly associated with higher risk for same-hospital readmission after the index Covid-19 admission (aHR 1.56, 95%CI 1.02-2.94).

**Discussion.**

This study presents data from 1024 patients with Covid-19 admitted to a teaching hospital in Alabama. Results of this study supports the safety of maintaining patients with chronic conditions on ACEis and ARBs during the Covid-19 pandemic and expands previous reports by demonstrating the protective effect of the ACEi/ARB from mortality in a racially diverse sample of patients with Covid-19. Among patients with hypertension, the use of ACEi/ARB prior to contracting Covid-19 was associated with a reduction in the likelihood of endotracheal intubation by nearly 40%. Further, ACEi/ARB use was not independently associated with greater need for ICU–level care or with an increase in the same-hospital readmissions.

Baseline use of ACEi/ARB was associated with 40% lower in-hospital mortality in patients with Covid-19, after controlling for potential confounders such as age, sex, race, obesity, smoking, and chronic medical conditions. These results were similar in the sample of patients who had any indication for RAAS inhibitors, and in patients with hypertension. Previous research has shown no association between the use of RAAS inhibitors and susceptibility to the Covid-19,[20] and has demonstrated the safety of continuing these medications during the pandemic[10,11,21]. Our study expands on previous findings by demonstrating both safety and reduction in Covid-19-related mortality, associated with RAAS inhibitor use in a racially diverse sample where 50% of patients were African American.

Half of the patients hospitalized with the Covid-19 infection in our sample were African Americans, whereas the proportion of African Americans in Alabama is only 26.7%. This finding highlights the racial disparity in the Covid-19 pandemic, in which a higher proportion of African Americans who developed severe Covid-19 infection, requiring hospitalization[22], compared to Whites. African American were also more likely to require iMV in our study. However, similar to other studies of COVID-19 outcomes in the US[23], race was not an independent predictor of death or hospital readmission in our study.

Our findings confirmed previous data that advanced age, obesity, and comorbidities are associated with death from Covid-19 [16,24]. Importantly, more than 30% of our patient sample admitted with severe Covid-19 had pre-existing heart failure, a rate almost ten times higher than the prevalence of heart failure in the general

population. Heart failure was also the only chronic condition, in addition to age and obesity in our sample, that was independently associated with increased in-hospital mortality from complications related to Covid-19. Patients with heart failure were also at increased risk of developing respiratory failure, requiring iMV. Patients with heart failure represent a particularly vulnerable group requiring special attention from healthcare to reduce mortality and morbidity from the Covid-19[25 26].

The rate of same-hospital readmissions among Covid-19 survivors was 19%, similar to a recent study of the patients with Covid-19, treated in the Veterans Affairs hospital system[27] but higher, compared to other reports estimating that only 3-10% of patients were re-hospitalized after the index Covid-19 admission[28,29]. The high rates of hospital readmission in our study sample may be explained by the high level of chronic disease prevalence and worse general health in the general population of Alabama. Importantly, diabetes was significantly associated with increased re-admission risk among Covid-19 survivors. Alabama has the third highest prevalence of diabetes among adults (14%) in the United States, according to the National Diabetes Statistics Report-2020 by the Centers of Disease Control. Our findings are likely to extend to states with a similar high prevalence of diabetes mellitus and underscore the importance of close outpatient follow-up of this at risk population.

Study limitations include limited geographical area and single hospital site. The data on out- of-hospital mortality and same-hospital readmissions may be incomplete as some Covid-19 patients may have been readmitted to other area hospitals. On average 30% of patients originally admitted to the UAB hospital can be re-admitted to other hospitals. The strengths of the study include a large racially diverse sample from the US Southeast, a region disproportionally affected by the Covid-19 and high prevalence of multiple medical comorbidities. We were able to develop a robust approach to extraction of data from medical records and assemble a cohort of the patients with Covid-19.

In conclusion, the use of RAAS inhibitors was associated with decreased in-hospital mortality from Covid-19 in this racially diverse sample. The RAAS inhibitors use was not associated with ICU-level care or hospital readmissions in the cohort of patients with Covid-19, while patients with diabetes were at a high risk

for same-hospital readmission. Among patients with hypertension, baseline RAAS inhibitor use was associated with a reduced risk of invasive mechanical ventilation. This study supports the continuation of RAAS inhibitors during the Covid-19 pandemic.

**Data availability statement.**

All data relevant to the study are available from the corresponding author on request.

**Ethics statements.**

The study procedures were approved by the UAB Institutional Review Board.

***Patient consent for publication:***

Not required.

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**Authors statement.**

YK deliniated project idea and design, conducted data analysis and drafted the manuscript.

GM conducted data management and alalysis.

YK, GM, JW had full access to data and ensured the accuracy or integrity of data.

All authors provided substantial contributions to the conception or design of the work; interpretation of data; revising the draft critically for important intellectual content; and final approval of the version to be published.

**Conflicts of interest.**

Dr. Cherrington reports serving as a consutant for Bayer. Dr Jackson reports research funding from NIH, and Amgen; editorial board membership: Circulation: Cardiovascular Quality and Outcomes; consulting: American College of Cardiology and McKesson, Inc.; Expert witness for DeBlase Brown Everly LLP.; and royalties for UpToDate. Dr. Safford reports research funding from Amgen. Dr. Oparil reports research funding from Bayer, CinCor Pharma Inc,George Medicine Pty Limited and Idorsia Pharmaceuticals. Other authors report no conflict of interest.

**Figure Legends.**

**Figure 1. Covid-19 In-Hospital Mortality, Hazard Ratio, 95% Confidence Intervals for ACEi/ARB Use.**

Legend. Figure 1 presents crude and adjusted hazards ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD,

history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

**Figure 2. Intensive Care Use, Odds Ratio, 95% CI for ACEi/ARB Use.**

Legend: Figure 2 presents crude and adjusted odds ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

**Figure 3. Respiratory Failure, requiring Invasive Mechanical Ventilation, Odd Ratio, 95% Confidence intervals, for ACEi/ARB Use**

Legend. Indications for ACEi/ARB use include hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020).

## References:


1. Fauci AS, Lane HC, Redfield RR. Covid-19 - Navigating the Uncharted. *N Engl J Med.* 2020;382(13):1268-1269.
2. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol.* 2020.
3. Porcheddu R, Serra C, Kelvin D, Kelvin N, Rubino S. Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. *J Infect Dev Ctries.* 2020;14(2):125-128.
4. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis.* 2020.
5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.
6. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation.* 2020;141(9):e139-e596.
7. Vuille-dit-Bille RN, Camargo SM, Emmenegger L, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. *Amino Acids.* 2015;47(4):693-705.
8. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *J Virol.* 2020;94(7).
9. Mackey K, King VJ, Gurley S, et al. Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults: A Living Systematic Review. *Ann Intern Med.* 2020;173(3):195-203.
10. Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med.* 2021.
11. Fosbol EL, Butt JH, Ostergaard L, et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. *JAMA.* 2020;324(2):168-177.
12. Shah P, Owens J, Franklin J, Jani Y, Kumar A, Doshi R. Baseline use of angiotensin-converting enzyme inhibitor/AT1 blocker and outcomes in hospitalized coronavirus disease 2019 African-American patients. *J Hypertens.* 2020;38(12):2537-2541.
13. Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension.* 2008;51(6):1624-1630.
14. Gu T, Mack JA, Salvatore M, et al. Characteristics Associated With Racial/Ethnic Disparities in COVID-19 Outcomes in an Academic Health Care System. *JAMA Netw Open.* 2020;3(10):e2025197.
15. Hippisley-Cox J, Young D, Coupland C, et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart.* 2020;106(19):1503-1511.
16. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA.* 2020;323(20):2052-2059.
17. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ.* 2020;371:m3731.
18. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical Characteristics of Covid-19 in New York City. *N Engl J Med.* 2020;382(24):2372-2374.
19. Goyal P, Ringel JB, Rajan M, et al. Obesity and COVID-19 in New York City: A Retrospective Cohort Study. *Ann Intern Med.* 2020;173(10):855-858.
20. Mehta N, Kalra A, Nowacki AS, et al. Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(9):1020-1026.
21. Lopes RD, Macedo AVS, de Barros ESPGM, et al. Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial. *JAMA.* 2021;325(3):254-264.

22. Chang MH, Moonesinghe R, Truman BI. COVID-19 Hospitalization by Race and Ethnicity: Association with Chronic Conditions Among Medicare Beneficiaries, January 1-September 30, 2020. *J Racial Ethn Health Disparities.* 2021.
23. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. *N Engl J Med.* 2020;382(26):2534-2543.
24. Levy TJ, Richardson S, Coppa K, et al. Development and Validation of a Survival Calculator for Hospitalized Patients with COVID-19. *medRxiv.* 2020.
25. Bhatt AS, Jering KS, Vaduganathan M, et al. Clinical Outcomes in Patients With Heart Failure Hospitalized With COVID-19. *JACC Heart Fail.* 2021;9(1):65-73.
26. Gorodeski EZ, Goyal P, Cox ZL, et al. Virtual Visits for Care of Patients with Heart Failure in the Era of COVID-19: A Statement from the Heart Failure Society of America. *J Card Fail.* 2020;26(6):448-456.
27. Donnelly JP, Wang XQ, Iwashyna TJ, Prescott HC. Readmission and Death After Initial Hospital Discharge Among Patients With COVID-19 in a Large Multihospital System. *JAMA.* 2021;325(3):304-306.
28. Lavery AM, Preston LE, Ko JY, et al. Characteristics of Hospitalized COVID-19 Patients Discharged and Experiencing Same-Hospital Readmission - United States, March-August 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(45):1695-1699.
29. Somani SS, Richter F, Fuster V, et al. Characterization of Patients Who Return to Hospital Following Discharge from Hospitalization for COVID-19. *J Gen Intern Med.* 2020;35(10):2838-2844.

Table 1. Characteristics of patients, admitted to UAB hospital with Covid-19, between March 1 and September 16, 2020

| | Overall sample, n=1024 | No ACEi/ARB Use, n=659 | ACEi/ARB use, n=365 | *P*-value |
|---|---|---|---|---|
| | n, (%) | n, (%) | n, (%) | |
| *Socio-Demographics* | | | | |
| **Age, mean, SD, years** | 57.0 (18.8) | 53.3 (19.7) | 63.7 (14.9) | <0.001 |
| **Age, categories, years** | | | | <0.001 |
| **18-40** | 241 (23.5) | 211 (32.0) | 30 (8.2) | |
| **41-64** | 395 (38.6) | 234 (35.5) | 161 (44.1) | |
| **65-74** | 202 (19.7) | 110 (16.7) | 92 (25.2) | |
| **75 and older** | 186 (18.2) | 104 (15.8) | 82 (22.5) | |
| **Race** | | | | <0.001 |
| **White** | 384 (37.5) | 254 (38.5) | 130 (35.6) | |
| **African American** | 532 (52.0) | 318 (48.3) | 214 (58.6) | |
| **Hispanic or Latino** | 63 (6.2) | 57 (8.6) | 6 (1.6) | |
| **Other** | 20 (2.0) | 12 (1.8) | 8 (2.2) | |
| **Declined to report** | 25 (2.4) | 18 (2.7) | 7 (1.9) | |
| **Male** | 514 (50.2) | 319 (48.4) | 195 (53.4) | 0.12 |
| **Married** | 414 (40.4) | 270 (41.0) | 144 (39.5) | 0.64 |
| **Smoking status** | | | | 0.09 |
| **Never** | 533 (59.6) | 344 (62.3) | 189 (55.1) | |
| **Current** | 98 (10.9) | 58 (10.5) | 40 (11.7) | |
| **Former** | 264 (29.5) | 150 (27.2) | 114 (33.2) | |
| *Comorbidities* | | | | |
| **Body Mass Index (BMI), kg/m2:** | | | | 0.24 |
| **Underweight, BMI < 18.5** | 27 (2.7) | 16 (2.5) | 11 (3.1) | |
| **Normal Weight, BMI=18.5-24** | 227 (22.5) | 159 (24.5) | 68 (18.9) | |
| **Overweight, BMI=25-30** | 268 (26.6) | 168 (25.8) | 100 (27.9) | |
| **Obese, BMI =30 and above** | 487 (48.3) | 307 (47.2) | 180 (50.1) | |
| **Hypertension** | 493 (48.1) | 204 (31.0) | 289 (79.2) | <.001 |
| **Coronary Artery Disease** | 340 (33.2) | 149 (22.6) | 191 (52.3) | <.001 |
| **Diabetes** | 210 (20.5) | 71 (10.8) | 139 (38.1) | <.001 |
| **COPD** | 138 (13.5) | 52 (7.9) | 86 (23.6) | <.001 |
| **Heart Failure** | 323 (31.5) | 131 (19.9) | 192 (52.6) | <.001 |

| | | | | |
|---|---|---|---|---|
| **Chronic Kidney Disease** | 325(31.7) | 139(21.1) | 186(51.0) | <.001 |
| **HIV** | 75 (7.3) | 24 (3.6) | 51 (14.0) | <.001 |
| **Sickle Cell Disease** | 10 (1.0) | 7 (1.1) | 3 (0.8) | 0.71 |
| **Recipient of solid organ transplant** | 40 (3.9) | 16 (2.4) | 24 (6.6) | 0.001 |
| | | | | |
| *Vital signs on presentation* | | | | |
| **Fever, Tmax > 100.4 $^0$F** | 343 (34.0) | 223 (34.5) | 120 (33.1) | 0.64 |
| **SBP, mean, SD, mmHg** | 128.5 (18.2) | 126.5 (17.1) | 132.1 (19.5) | <0.001 |
| **SBP < =100 mmHg** | 311 (30.8) | 207 (32.0) | 104 (28.6) | 0.25 |
| **Heart rate >100 beat/min** | 515 (50.6) | 357 (54.7) | 158 (43.4) | 0.001 |
| **Respiratory rate => 22 breath/min** | 622 (61.2) | 403 (61.7) | 219 (60.3) | 0.66 |
| *Laboratory data on presentation, mean, SD* | | | | |
| **Leukocytes x10$^9$ cells/L** | 8.5 (4.9) | 8.9 (5.2) | 7.9 (4.0) | 0.002 |
| **Platelets x10$^9$ cells/L** | 227.4(101.1) | 235.1(111.8) | 213.3 (76.0) | 0.002 |
| **Serum creatinine, mg/dL** | 1.7 (2.0) | 1.3 (1.3) | 2.2( 2.7) | <0.001 |
| **Aspartate aminotransferase U/L** | 88.3(484.8) | 90.0(502.6) | 85.3(453.2) | 0.91 |
| **Alanine aminotransferase U/L** | 53.4(193.8) | 54.9(172.6) | 50.9(225.4) | 0.81 |
| **Total Bilirubin, mg/dL** | 0.8 (1.1) | 0.9 (1.3) | 0.7(0.6) | 0.11 |
| *In-hospital Events** | | | | |
| **Admission after July 15, 2020** | 621 (60.6) | 398(60.4) | 223(61.1) | 0.83 |
| **Required Intensive Care Unit** | 466 (45.5) | 287 (43.6) | 179 (49.0) | 0.09 |
| **Invasive mechanical ventilation** | 276 (27.0) | 179 (27.2) | 97 (26.6) | 0.84 |
| **In-hospital Death** | 137(13.4) | 96 (14.6) | 41(11.2) | 0.13 |
| *Post-Discharge events among the survivors of the index admission* | n=877 | n=563 | n=324 | |
| **All-cause same-hospital readmission (during March 1-September 16,2020)** | 170 (19.2) | 97 (16.7) | 76 (23.5) | 0.01 |
| **Death from any cause after index admission** | 16(1.8) | 9(1.0) | 7(2.2) | 0.54 |
| **Cumulative Mortality (death during March 1-September 16,2020)** | 153 (14.9) | 105 (15.9) | 48 (13.2) | 0.23 |

Abbreviations: ACEi – Angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, COPD – chronic obstructive pulmonary disease, SBP- systolic blood pressure, SD – standard deviation

Table 2. Factors, associated with in-hospital mortality among patients with Covid-19, admitted to UAB hospital, between March 1 and September 16, 2020. Multivariable-adjusted Cox proportional hazards regression model.

| | HR | 95% CI | | *P*-value |
|---|---|---|---|---|
| ACEi/ARB Use | 0.56 | 0.36 | 0.88 | 0.01 |
| **Age, years:** | | | | <0.001 |
| **18-40** | ref | - | - | - |
| **40-64** | 1.69 | 0.82 | 3.52 | |
| **65-74** | **4.07** | **2.10** | **9.24** | |
| **75 and older** | **5.53** | **2.52** | **12.14** | |
| **Race:** | | | | 0.55 |
| **African American** | 0.88 | 0.60 | 1.29 | |
| **Hispanic/Latino/Asian/Other** | 0.68 | 0.32 | 1.45 | |
| **White** | ref | | | |
| **Male** | 1.43 | 0.97 | 2.10 | 0.07 |
| **Married** | 0.91 | 0.63 | 1.34 | 0.64 |
| **Current Smoker** | 1.04 | 0.51 | 2.14 | 0.91 |
| **Body Mass Index, kg/m2:** | | | | 0.001 |
| **< 18.5** | 1.91 | 0.63 | 5.79 | |
| **18.5-24** | ref | | | |
| **25-29** | 1.39 | 0.81 | 2.37 | |
| **30 and above** | **2.50** | **1.54** | **4.06** | |
| **Hypertension** | 0.91 | 0.52 | 1.57 | 0.73 |
| **Coronary Artery Disease** | 0.78 | 0.57 | 1.20 | 0.26 |
| **Chronic Kidney Disease** | 0.87 | 0.54 | 1.38 | 0.54 |
| **Heart Failure** | **1.96** | **1.21** | **3.15** | **0.006** |
| **Diabetes** | 1.07 | 0.62 | 1.84 | 0.98 |
| **COPD** | 1.07 | 0.58 | 1.95 | 0.84 |
| **HIV** | 1.51 | 0.76 | 3.03 | 0.23 |
| **Solid organ transplant recipient** | 1.56 | 0.61 | 3.96 | 0.35 |

Abbreviations: ACEi – Angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, CI-confidence interval, COPD – chronic obstructive pulmonary disease, HR- hazard ratio.

Table 3. Factors associated with same-hospital readmission among patients with Covid-19, between March 1 and September 16, 2020. Multivariable-adjusted Cox proportional hazards regression model. Death after index admission is accounted as a completing risk.

| | SHR | 95% CI | | p-value |
|---|---|---|---|---|
| **Use of ACEi/ARB** | 1.19 | 0.82 | 1.72 | 0.37 |
| **Age, years:** | | | | 0.23 |
| **18-40** | ref | - | - | - |
| **40-64** | 0.90 | 0.59 | 1.37 | |
| **65-74** | 0.75 | 0.44 | 1.27 | |
| **75 and older** | 0.54 | 0.29 | 1.01 | |
| **Race:** | | | | 0.04 |
| **African American** | 1.11 | 0.78 | 1.60 | |
| **Hispanic/Latino/Asian/Other** | **0.42** | **0.20** | **0.90** | |
| **White** | ref | | | |
| **Male** | 1.01 | 0.71 | 1.43 | 0.95 |
| **Married** | 1.32 | 0.94 | 1.86 | 0.11 |
| **Current Smoker** | 0.70 | 0.40 | 1.20 | 0.19 |
| **Body Mass Index, kg/m2:** | | | | 0.05 |
| **< 18.5** | 1.20 | 0.53 | 2.71 | |
| **18.5-24** | ref | | | |
| **25-29** | 0.69 | 0.44 | 1.07 | |
| **30 and above** | **0.59** | **0.39** | **0.90** | |
| **Hypertension** | 0.84 | 0.51 | 1.38 | 0.48 |
| **Coronary Artery Disease** | 0.87 | 0.58 | 1.29 | 0.47 |
| **Chronic Kidney Disease** | 1.19 | 0.76 | 1.86 | 0.46 |
| **Heart Failure** | 1.41 | 0.92 | 2.16 | 0.11 |
| **Diabetes** | **1.56** | **1.02** | **2.39** | **0.04** |
| **COPD** | 1.28 | 0.76 | 2.14 | 0.36 |
| **HIV** | 0.92 | 0.50 | 1.70 | 0.79 |
| **Solid organ transplant recipient** | 0.84 | 0.39 | 1.81 | 0.66 |

Abbreviations: ACEi – Angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, CI-confidence interval, COPD – chronic obstructive pulmonary disease, SHR- sub-hazard ratio.

**Bold p-value < .05**

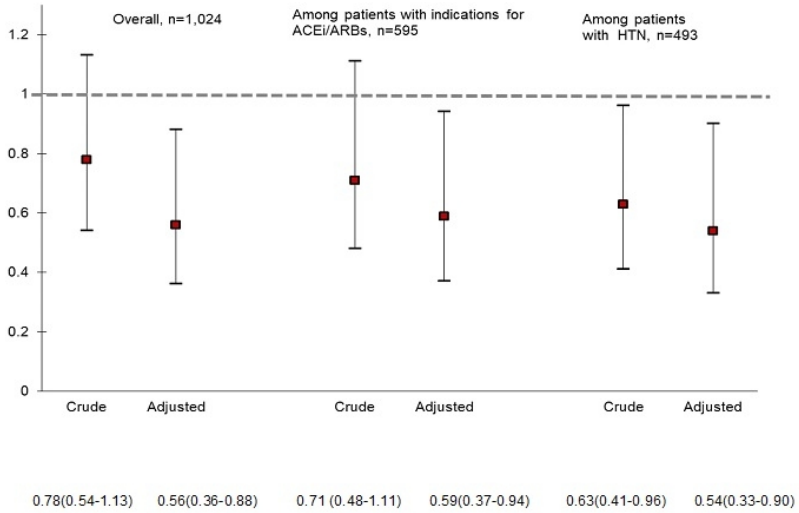


Figure 1. Covid-19 In-Hospital Mortality, Hazard Ratio, 95% Confidence Intervals for ACEi/ARB Use.
Legend. Figure 1 presents crude and adjusted hazards ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

224x153mm (96 x 96 DPI)

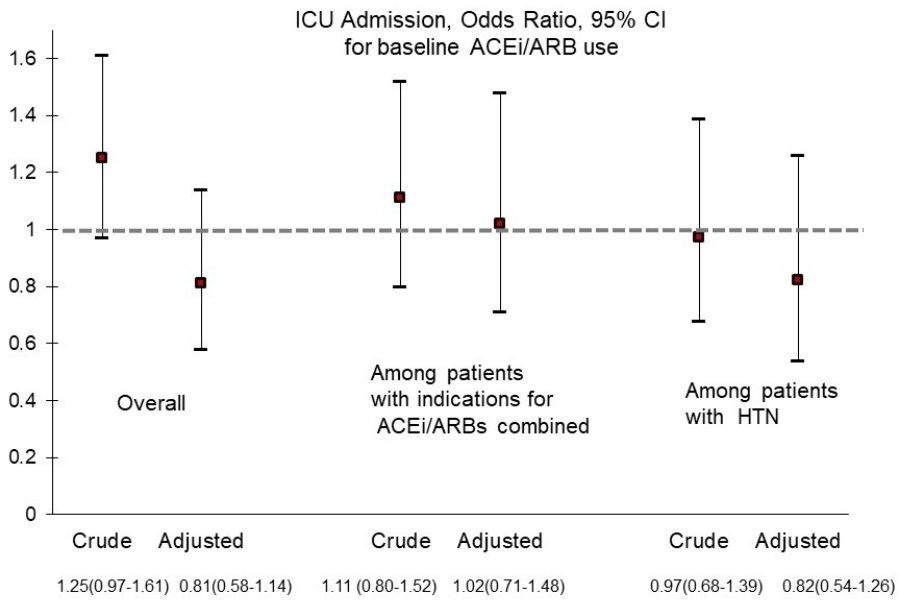


Figure 2. Intensive Care Use, Odds Ratio, 95% CI for ACEi/ARB Use.
Legend: Figure 2 presents crude and adjusted odds ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

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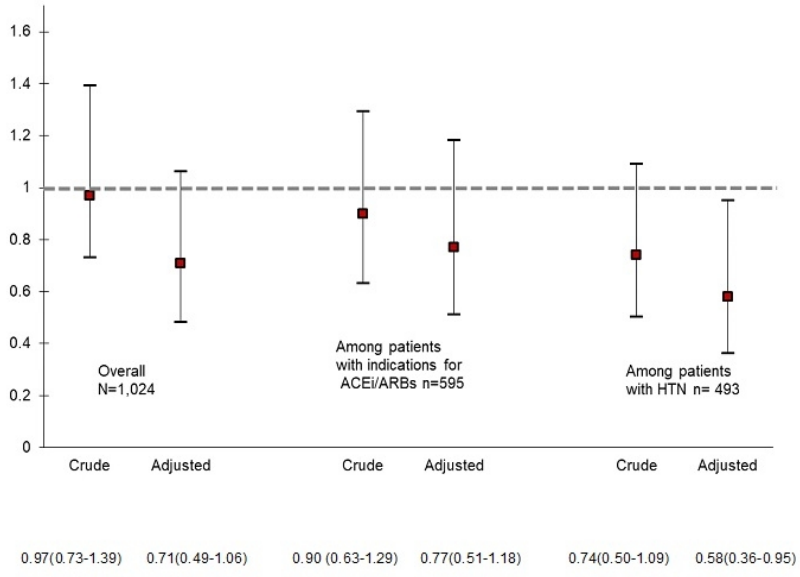


Figure 3. Respiratory Failure, requiring Invasive Mechanical Ventilation, Odd Ratio, 95% Confidence intervals, for ACEi/ARB Use

Legend. Indications for ACEi/ARB use include hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020).

222x145mm (96 x 96 DPI)

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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| | | Reporting Item | Page Number |
|---|---|---|---|
| **Title and abstract** | | | |
| Title | #1a | Indicate the study's design with a commonly used term in the title or the abstract | 2 |

| | | | |
|---|---|---|---|
| Abstract | #1b | Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background / rationale | #2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | #3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | #4 | Present key elements of study design early in the paper | 4 |
| Setting | #5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 |
| Eligibility criteria | #6a | Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. | 4 |
| Eligibility criteria | #6b | For matched studies, give matching criteria and number of exposed and unexposed | n/a |
| Variables | #7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4 |
| Data sources / measurement | #8 | For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than | 5 |

| | | | |
|---|---|---|---|
| | | one group. Give information separately for for exposed and unexposed groups if applicable. | |
| Bias | #9 | Describe any efforts to address potential sources of bias | 5 |
| Study size | #10 | Explain how the study size was arrived at | 4 |
| Quantitative variables | #11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | 5 |
| Statistical methods | #12a | Describe all statistical methods, including those used to control for confounding | 5 |
| Statistical methods | #12b | Describe any methods used to examine subgroups and interactions | 5 |
| Statistical methods | #12c | Explain how missing data were addressed | 5 |
| Statistical methods | #12d | If applicable, explain how loss to follow-up was addressed | n/a |
| Statistical methods | #12e | Describe any sensitivity analyses | n/a |
| **Results** | | | |
| Participants | #13a | Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed | 6 |

| | | | |
|---|---|---|---|
| | | eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable. | |
| Participants | #13b | Give reasons for non-participation at each stage | n/a |
| Participants | #13c | Consider use of a flow diagram | |
| n/a | | | |
| Descriptive data | #14a | Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable. | 6 |
| Descriptive data | #14b | Indicate number of participants with missing data for each variable of interest | |
| 6 | | | |
| Descriptive data | #14c | Summarise follow-up time (eg, average and total amount) | |
| 7 | | | |
| Outcome data | #15 | Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable. | |
| 7 | | | |

| | | | |
|---|---|---|---|
| Main results | #16a | Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 7,8 |
| Main results | #16b | Report category boundaries when continuous variables were categorized | 6 |
| Main results | #16c | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| n/a | | | |
| Other analyses | #17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 7,8 |
| **Discussion** | | | |
| Key results | #18 | Summarise key results with reference to study objectives | 8 |
| Limitations | #19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. | 9 |
| Interpretation | #20 | Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. | 9 |
| Generalisability | #21 | Discuss the generalisability (external validity) of the study results | 10 |
| **Other Information** | | | |

| | | | |
|---|---|---|---|
| Funding | #22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 11 |

BMJ Open

# What is the Effect of Renin-Angiotensin-Aldosterone System Inhibitors in a Racially Diverse Patients, Hospitalized with Covid-19?



| | |
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# What is the Effect of Renin-Angiotensin-Aldosterone System Inhibitors in a Racially Diverse Patients, Hospitalized with Covid-19?

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**Abstract.**

**Objective:** To describe the clinical outcomes of Covid-19 in a racially diverse sample from the US Southeast and examine the association of renin-angiotensin-aldosterone system (RAAS) inhibitor use with Covid-19 outcome.

**Design, Setting, Participants:** This study is a retrospective cohort of 1,024 patients with reverse-transcriptase–polymerase-chain-reaction-confirmed Covid-19 infection, admitted to a 1,242-bed teaching hospital in Alabama. Data on RAAS inhibitors use, demographics and comorbidities were extracted from hospital medical records.

**Primary Outcome**s: In-hospital mortality, a need of intensive care (ICU), respiratory failure, defined as invasive mechanical ventilation (iMV), and 90-day same-hospital readmissions.

**Results:** Among 1024 patients (mean [SD] age, 57 [18.8] years), 532 [52.0%] were African Americans, 514 [50.2%] male, 493 [48.1%] had hypertension, 365 [36%] were taking RAAS inhibitors. During index hospitalization (median length of stay of 7 (interquartile range [4-15]) days) 137(13.4%) patients died; 170(19.2%) of survivors were re-admitted. RAAS inhibitor use was associated with lower in-hospital mortality (adjusted hazard ratio, 95%CI [0.56, (0.36-0.88), *P*=0.01) and no effect modification by race was observed (*P* for interaction = 0.81). Among patients with hypertension, baseline RAAS use was associated with reduced risk of iMV, adjusted odds ratio, 95% CI [aOR=0.58, 95%CI (0.36-0.95), *P*=0.03]. Patients with heart failure were twice as likely to die from Covid-19, compared to patients without heart failure.

**Conclusions:** Among racially diverse patients, hospitalized with Covid-19, pre-hospitalization use of RAAS inhibitors was associated with 40% reduction in mortality irrespective of race.

**Article summary.**

**Strength and limitations.**

- This study background was based on multiple questions on RAAS safety, raised by the community of the primary care physicians and patients in the beginning of the COVID-19 pandemic.
- Other strengths of the study include a large racially diverse sample of patients with COVID-19 from the US Southeast and a robust approach to extraction of data from electronic health records.
- Observational retrospective nature of this study does not allow drawing causal inferences.
- The study included patients from a limited geographical area and a single hospital site.
- The data on out- of-hospital mortality and same-hospital readmissions may be incomplete as some Covid-19 patients may have been readmitted to other area hospitals.

**Introduction.**

The United States has experienced an unprecedented public health crisis with the Covid-19 pandemic.[1] Persons with cardiovascular and metabolic disease are at increased risk for mortality and morbidity from Covid-19[2-5]. Cardiovascular disease and diabetes mellitus are highly prevalent among US adults, with 45% of adults having HTN, 13% - diabetes mellitus, 6.7% - coronary artery disease, and 2.4% - heart failure[6]. These chronic conditions disproportionally affect adults in the Southeast compared to other parts of the US[6]. Patients with hypertension, heart failure, diabetes, and chronic kidney disease are often prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors, i.e., angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). In animal studies, performed prior to the emergence of Covid-19, ACEi were found to increase the expression of ACE2 receptors.[7] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to ACE2 receptors in lungs[8], leading to concerns about potential risks of utilizing RAAS inhibitors in the setting of Covid-19. While subsequent studies have demonstrated the safety of RAAS inhibitor use among persons with Covid-19 and indication for RAAS use[9-11], the association of RAAS inhibitor use with hospital readmission after the index Covid-19 admission is not well described.

Most of reports[12] describing the associations of pre-existing use of RAAS inhibitors with COVID-19 outcomes were obtained in White or Asian, not African American populations. Compared to Whites, African Americans have a high incidence of adverse effects of RAAS inhibitors [13]. Disproportionally affected by multiple health disparities, African Americans have also been shown to have an increased risk of severe COVID-19, requiring hospitalization[14]. Persons of African descent were also at higher risk of contracting COVID-19 in the largest to date cohort study of the Covid-19 susceptibility in England[15].

To better understand the association of baseline RAAS inhibitor use with outcomes of Covid-19 hospitalization, we assembled an observational retrospective cohort of racially diverse hospitalized patients with laboratory-confirmed Covid-19 in Alabama. We examined whether baseline RAAS inhibitor use was associated with Covid-19 health outcomes, including 1) in-hospital mortality, 2) need for Intensive Care Unit (ICU)

admission 3) acute respiratory failure requiring intubation and mechanical ventilation (iMV), and 4) same-hospital readmission for any cause among survivors of the Covid-19 index hospitalization. We also assessed whether the association between RAAS inhibitor use and mortality differed by race.

**Methods.**

**Study participants and procedures.**

This observational retrospective cohort study included 1024 adult (age 18 and above) patients hospitalized with confirmed Covid-19 between March 1 and September 16, 2020 at the University of Alabama at Birmingham (UAB) teaching hospital in Birmingham, Alabama. The first cases of the Covid-19 were detected in Birmingham beginning on March 1, 2020. The cases increased very slowly over the spring of 2020, with a sharp surge 10-14 days after July 4, 2020. After the initial surge, Covid-19 cases declined slightly in August 2020, but then started to rise, achieving an spike in December-January 2021 (data not included in this report). The UAB ICU neared but did not exceed capacity. During the first surge of Covid-19 cases in July 2020, UAB Hospital implemented a delayed intubation strategy, favoring treating Covid-19 respiratory failure with supplemental oxygen, delivered via high flow nasal cannula. Therefore, all analyses of respiratory failure were adjusted for the time of the index admission for Covid-19 (before vs. after July 15, 2020).

Covid-19 cases were confirmed by reverse-transcriptase polymerase chain-reaction testing (rt-PCR). We extracted patient data electronically from our institution's Electronic Health Record (EHR; Cerner) data warehouse (i2B2) supplemented by manual chart review. Data were prepared for analyses by the COVID Core data Extraction/Transformation team using Oracle SQL developer (v.11.2). For each of the patients with lab-confirmed Covid-19, encounter data for the index admission were obtained, including admission date, date of the earliest positive rt-PCR for Covid-19 and death or discharge date. The admission/discharge dates for all subsequent outpatient and inpatient encounters and dates of death after the index hospitalization were also electronically extracted. For each of the hospital readmissions (n=172) a manual chart review was conducted to confirm admission/discharge dates. For each of the deaths (n=16) that occurred after index hospitalization we conducted manual chart review for confirmation. From the initial sample of 1029 patients, we excluded 5

patients with missing index admission dates or missing dates of birth. The study procedures were approved by the UAB Institutional Review Board.

**Patient and public Involvement.**

No patient involved.

**Outcomes and main exposure.**

Study outcomes included in-hospital Covid-19-related mortality, need for the ICU admission, respiratory failure defined by a need for invasive mechanical ventilation, and same-hospital readmission for any cause after the index hospitalization. Data on RAAS inhibitors included use of ACEis and ARBs prior to the index Covid-19 hospitalization, and were derived from the index admission medication reconciliation data in the EHR. If patients were taking a combination medicine that included an ACEi or ARB as one of the components, they were classified as having been prescribed ACEi/ARB in the analysis.

**Covariates.**

Covariates were selected on the basis of the risk factors for severe Covid-19 infection identified by the Centers for Disease Control and Prevention and previous reports on Covid-19 morbidity and mortality [16-19]. Patient socio-demographic characteristics included age at the index admission (calculated, using birth and admission dates) and self-reported race, sex, marital status, and cigarette smoking status. We created age categories as follows: 18-40, 41-64, 65-74, and 75 years and older. Body mass index (BMI) was calculated using height and weight obtained most recently prior to the index Covid-19 admission. BMI categories included: "underweight" is less than 18.5 kg/m$^2$, "normal weight" 18.5-24.9 kg/m$^2$, "overweight" 25-29.9 kg/m$^2$ and "obese" 30 kg/m$^2$,and above. We obtained data on comorbidities, including hypertension, coronary artery disease, diabetes, chronic obstructive pulmonary disease (COPD), heart failure, chronic kidney disease, HIV, sickle cell disease, and history of solid organ transplant using corresponding ICD-10 codes.

**Statistical Analysis.**

Patients with Covid-19 who were prescribed RAAS inhibitors at baseline were compared to those who were not prescribed RAAS inhibitors using two-sided t-tests for continuous variables and Chi-square tests for

categorical variables. We examined the association of RAAS inhibitor use with study outcomes in three different samples: 1) overall sample, 2) patients with any indication for RAAS inhibitor use, such as hypertension, diabetes, chronic kidney disease, coronary artery disease or heart failure and 3) patients with hypertension. Outcomes were assessed with unadjusted and multivariable models. To examine the association of in-hospital mortality from Covid-19 with baseline RAAS inhibitor use we constructed Cox proportional hazards regression models adjusted for age, sex, race, marital status, smoking, BMI, and medical conditions. We created an interaction term between RAAS use and race to test for effect modification by race in the fully adjusted models of Covid-19 in-hospital mortality. The need for ICU and the presence of respiratory failure were examined separately in logistic regression models, with adjustment for the same patient characteristics and for the time of admission (before vs. after July 15, 2020).

We examined the charts of the survivors of the index Covid-19 admission post-discharge for a same-hospital readmission for any cause using medical records. The EHR data were abstracted for any subsequent in-hospital and outpatient encounter after the index hospitalization and UAB hospital readmission dates were extracted. The time to readmission was calculated using index discharge data and readmission date. To examine the association between baseline RAAS use and readmissions, we used the Fine and Gray Model to account for competing risk of death in the post-discharge period that was adjusted for the same patient characteristics. The proportionality assumption was tested and satisfied in the Cox proportion hazards models. All statistical analyses were performed in SAS software (SAS Institute, Cary, NC) version 9.4,

**Results.**

Among 1024 patients, admitted to UAB hospital with Covid-19 (mean [SD] age, 57 [18.8] years), 532 [52%] were African American, 514 [50 %] were male, 493 [48 %] had hypertension, 323 [32 %] had heart failure, 487 [48 %] were obese, 210 [20.5%] had diabetes and 98 [11 %] were current smokers (Table 1). There were 365 [36%] patients taking RAAS inhibitors at baseline. Patients with baseline RAAS use were older, more likely to be African American, and had more comorbidities.

The median length of stay (LOS) for the index Covid-19 hospitalization was 7 days, [interquartile range (IQR) 4-15 days]. Maximum LOS was 175 days. Sixty percent of included Covid-19 cases were admitted after the initial surge in Birmingham, between July 15 and September 16, 2020. During the index hospitalization, 137 (13.4%) patients died. Additionally, 16 (1.8%) patients died from any cause post-discharge, either during a hospital readmission or out of the hospital. Cumulative all-cause mortality included 153 (14.9%) deaths. At the time of the cohort assembly on September 16, 2020, 23 patients remained in the hospital. During the index hospitalization 466 (45.5%) patients required ICU care, and 276 (27%) persons required iMV. The proportion of patients who were intubated was higher in the early period, before July 15, compared to the period of after July 15,2020, when placing the patient with respiratory failure on high flow nasal canula became a preferred treatment strategy: 201 [32.4%] vs. 75 [ 18.6], *P* <.001.

**In-hospital Covid-19 mortality and RAAS use.**

The median time to death was 13 days [IQR 6-20 days]. In the overall study sample, baseline RAAS inhibitor use was associated with significantly reduced risk of in-hospital mortality (adjusted hazard ratio [aHR] 0.56, 95% confidence interval [95%CI] 0.36-0.88], *P*=0.01, after adjustment for all covariates) (Figure 1). A similar protective effect of RAAS inhibitor use on mortality was observed among patients with any indication for RAAS inhibitor use (aHR [95%CI] for RAAS inhibitor use 0.59, 95%CI 0.37-0.94, *P*=0.03) and among patients with hypertension (aHR for RAAS use 0.54, 95%CI 0.33-0.90, *P*=0.02). We did not observe effect modification by race in the overall sample. The RAAS inhibitor use*race interaction term had associated *P*= 0.81. Compared to Whites, African American race was not associated with in-hospital mortality from Covid-19 in the adjusted model (aHR 0.88, 95% CI 0.60-1.29, *P* for trend 0.55) (Table 2). Other factors associated with increased cumulative mortality in our sample included age 65-74 years (aHR 3.67 [95%CI 1.85-7.31]), age 75 years and older (aHR 4.89 [95%CI 2.36-10.14]), obesity (aHR 2.10 [95%CI 1.34-3.29]), and pre-existing heart failure (aHR 1.88 [95%CI 1.20-2.94]) (Table 2).

**Covid-19 in-hospital events and RAAS inhibitor use.**

RAAS inhibitor use was not associated with the need for ICU in all analyses (Figure 2.) In the overall patient sample, RAAS use was not associated with iMV, aOR 0.71[95%CI 0.48-1.06] (Figure 3). In contrast, among patients with hypertension, baseline RAAS inhibitor use was significantly associated with reduced odds of iMV after adjustment for covariates (aOR 0.58 [95%CI 0.36-0.95], *P*=.03). African Americans admitted with Covid-19 were more likely to have respiratory failure, requiring iMV: aOR 1.58 [95%CI 1.01-2.31], *P*=.02. Other factors associated with the increased risk of iMV for the Covid-19-related respiratory failure included current cigarette smoking (aOR 1.80 [95%CI 1.08-3.02], *P*=.03), pre-existing heart failure (aOR 2.32 [95%CI 1.45-3.71], *P* <.001) and being admitted to UAB before July 15, 2020 (aOR 1.97 [95%CI 1.39-2.79], *P* <.0010.

**Same-hospital 90-day readmissions among Covid-19 survivors.**

Over a median follow up of 51 [IQR 28-82] days, 170 (19.2%) of 887 discharged patients were readmitted to the same hospital for any cause (Table 1). Among those who were re-hospitalized, the median time to readmission following the index discharge was 10 days [IQR 4-29 days]. The proportion of persons with same-hospital readmission among those with baseline RAAS inhibitor use was 23.5%, compared to 16.7% among those who were not prescribed RAAS inhibitors *(P*=0.01) (Table 1). In the fully adjusted Cox proportional models, accounting for death as a competing risk, baseline RAAS agent use was not associated with readmissions (Table 3). Compared to White patients, patients of the Hispanic/Latino/Asian or other race/ethnicity were less likely to be readmitted (aHR 0.42, 95% CI 0.20-0.90). African-American race was not statistically significantly associated with hospital readmission (aHR 1.11, 95% CI 0.78-1.60). Among the chronic medical conditions only diabetes was significantly associated with higher risk for same-hospital readmission after the index Covid-19 admission (aHR 1.56, 95%CI 1.02-2.94).

## Discussion.

This study presents data from 1024 patients with Covid-19 admitted to a teaching hospital in Alabama. Results of this study support the safety of maintaining patients with chronic conditions on ACEis and ARBs during the Covid-19 pandemic and expands previous reports by demonstrating the protective effect of the ACEis/ARBs from mortality in a racially diverse sample of patients with Covid-19. Among patients with

hypertension, the use of ACEis/ARsB prior to contracting Covid-19 was associated with a reduction in the likelihood of endotracheal intubation by nearly 40%. Further, ACEi/ARB use was not associated with greater need for ICU–level care or with an increase in the same-hospital readmissions.

Baseline use of ACEi/ARB was associated with 40% lower in-hospital mortality in patients with Covid-19, after controlling for potential confounders such as age, sex, race, obesity, smoking, and chronic medical conditions. These results were similar in the sample of patients who had any indication for RAAS inhibitors, and in patients with hypertension. Previous research has shown no association between the use of RAAS inhibitors and susceptibility to the Covid-19,[20] and has demonstrated the safety of continuing these medications during the pandemic[10,11,21]. Similary to our results, in 1.4 million patients with hypertension, heart failure, diabetes, kidney disease, or ischemic heart disease registered in the Swedish National Patient Registry, ACEi/ARB use was associated with a reduced mortality in COVID-19 cases (aHR 0.89, 95% CI [0.82-0.96])[22]. Our study expands on previous findings by demonstrating both safety and reduction in Covid-19-related mortality associated with RAAS inhibitor use in a racially diverse sample where 50% of patients were African American.

Half of the patients hospitalized with the Covid-19 infection in our sample were African American, whereas the proportion of African Americans in Alabama is only 26.7%. This finding highlights the racial disparity in the Covid-19 pandemic, in which a higher proportion of African Americans developed severe Covid-19 infection, requiring hospitalization[23], compared to Whites. African Americans were also more likely to require iMV in our study. However, similar to other studies of COVID-19 outcomes in the US[24], race was not an independent predictor of death or hospital readmission in our study.

Our findings confirm previous observations that advanced age, obesity, and comorbidities are associated with death from Covid-19 [16,25]. Importantly, more than 30% of our patient sample admitted with severe Covid-19 had pre-existing heart failure, a rate almost ten times higher than the prevalence of heart failure in the general population. Heart failure was the only chronic condition, in addition to age and obesity in our sample, that was independently associated with increased in-hospital mortality from complications related to Covid-19.

Patients with heart failure were also at increased risk of developing respiratory failure, requiring iMV. These represent a particularly vulnerable group requiring special attention from healthcare to reduce mortality and morbidity from the Covid-19[26 27].

The rate of same-hospital readmissions among Covid-19 survivors was 19%, similar to that in a recent study of the patients with Covid-19, treated in the Veterans Affairs hospital system[28] but higher, than in other reports estimating that only 3-10% of patients were re-hospitalized after the index Covid-19 admission[29,30]. The high rates of hospital readmission in our study sample may be explained by the high level of chronic disease prevalence and worse general health in the general population of Alabama. Importantly, diabetes was significantly associated with increased re-admission risk among Covid-19 survivors. Alabama has the third highest prevalence of diabetes among adults (14%) in the United States, according to the National Diabetes Statistics Report-2020 by the Centers of Disease Control. Our findings are likely to extend to states with a similar high prevalence of diabetes mellitus and underscore the importance of close outpatient follow-up of this at risk population.

Study limitations include limited geographical area and single hospital site. The data on out- of-hospital mortality and same-hospital readmissions may be incomplete, as some Covid-19 patients may have been readmitted to other area hospitals. On average 30% of patients originally admitted to the UAB hospital are re-admitted to other hospitals. The observational retrospective nature of this study does not allow drawing causal inferences. EHR data regarding pre-existing medical conditions and smoking may be incomplete. Strengths of the study include a large racially diverse sample from the US Southeast, a region disproportionally affected by Covid-19 and high prevalence of multiple comorbidities. Further, we were able to develop a robust approach to extraction of data from EHR and assemble a cohort of the patients with Covid-19.

In conclusion, use of RAAS inhibitors was associated with decreased in-hospital mortality from Covid-19 in this racially diverse sample. RAAS inhibitor use was not associated with ICU-level care or hospital readmissions in the cohort of patients with Covid-19, while patients with diabetes were at a high risk for same-hospital readmission. Among patients with hypertension, baseline RAAS inhibitor use was associated with a

reduced risk of invasive mechanical ventilation. This study supports the continuation of RAAS inhibitors during the Covid-19 pandemic.

**Data availability statement.**

All data relevant to the study are available from the corresponding author on request.

**Ethics statements.**

The study procedures were approved by the UAB Institutional Review Board.

***Patient consent for publication:***

Not required.

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**Authors statement.**

YK delineated project idea and design, conducted data analysis and drafted the manuscript.

YK, GM conducted data management and analysis.

YK, GM, JW had full access to data and ensured the accuracy or integrity of data.

SC, RF, MS, PG, SO, AC, EAJ edited and revised the manuscript.

All authors provided substantial contributions to the conception or design of the work; interpretation of data; revising the draft critically for important intellectual content; and final approval of the version to be published.

**Conflicts of interest.**

Dr. Cherrington reports serving as a consultant for Bayer. Dr Jackson reports research funding from NIH, and Amgen; editorial board membership: Circulation: Cardiovascular Quality and Outcomes; consulting: American College of Cardiology and McKesson, Inc.; Expert witness for DeBlase Brown Everly LLP.; and royalties for UpToDate. Dr. Safford reports research funding from Amgen. Dr. Oparil reports research funding from Bayer, CinCor Pharma Inc, George Medicine Pty Limited and Idorsia Pharmaceuticals. Other authors report no conflict of interest.

**Figure Legends.**

**Figure 1. Covid-19 In-Hospital Mortality, Hazard Ratio, 95% Confidence Intervals for ACEi/ARB Use.**

Legend. Figure 1 presents crude and adjusted hazards ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD,

history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

**Figure 2. Intensive Care Use, Odds Ratio, 95% CI for ACEi/ARB Use.**

Legend: Figure 2 presents crude and adjusted odds ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

**Figure 3. Respiratory Failure, requiring Invasive Mechanical Ventilation, Odd Ratio, 95% Confidence intervals, for ACEi/ARB Use**

Legend. Indications for ACEi/ARB use include hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020).

## References:


1. Fauci AS, Lane HC, Redfield RR. Covid-19 - Navigating the Uncharted. *N Engl J Med.* 2020;382(13):1268-1269.
2. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol.* 2020.
3. Porcheddu R, Serra C, Kelvin D, Kelvin N, Rubino S. Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. *J Infect Dev Ctries.* 2020;14(2):125-128.
4. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis.* 2020.
5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.
6. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation.* 2020;141(9):e139-e596.
7. Vuille-dit-Bille RN, Camargo SM, Emmenegger L, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. *Amino Acids.* 2015;47(4):693-705.
8. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *J Virol.* 2020;94(7).
9. Mackey K, King VJ, Gurley S, et al. Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults: A Living Systematic Review. *Ann Intern Med.* 2020;173(3):195-203.
10. Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med.* 2021.
11. Fosbol EL, Butt JH, Ostergaard L, et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. *JAMA.* 2020;324(2):168-177.
12. Shah P, Owens J, Franklin J, Jani Y, Kumar A, Doshi R. Baseline use of angiotensin-converting enzyme inhibitor/AT1 blocker and outcomes in hospitalized coronavirus disease 2019 African-American patients. *J Hypertens.* 2020;38(12):2537-2541.
13. Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension.* 2008;51(6):1624-1630.
14. Gu T, Mack JA, Salvatore M, et al. Characteristics Associated With Racial/Ethnic Disparities in COVID-19 Outcomes in an Academic Health Care System. *JAMA Netw Open.* 2020;3(10):e2025197.
15. Hippisley-Cox J, Young D, Coupland C, et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart.* 2020;106(19):1503-1511.
16. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA.* 2020;323(20):2052-2059.
17. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ.* 2020;371:m3731.
18. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical Characteristics of Covid-19 in New York City. *N Engl J Med.* 2020;382(24):2372-2374.
19. Goyal P, Ringel JB, Rajan M, et al. Obesity and COVID-19 in New York City: A Retrospective Cohort Study. *Ann Intern Med.* 2020;173(10):855-858.
20. Mehta N, Kalra A, Nowacki AS, et al. Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(9):1020-1026.
21. Lopes RD, Macedo AVS, de Barros ESPGM, et al. Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial. *JAMA.* 2021;325(3):254-264.

22. Savarese G, Benson L, Sundstrom J, Lund LH. Association between renin-angiotensin-aldosterone system inhibitor use and COVID-19 hospitalization and death: a 1.4 million patient nationwide registry analysis. *Eur J Heart Fail.* 2021;23(3):476-485.
23. Chang MH, Moonesinghe R, Truman BI. COVID-19 Hospitalization by Race and Ethnicity: Association with Chronic Conditions Among Medicare Beneficiaries, January 1-September 30, 2020. *J Racial Ethn Health Disparities.* 2021.
24. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. *N Engl J Med.* 2020;382(26):2534-2543.
25. Levy TJ, Richardson S, Coppa K, et al. Development and Validation of a Survival Calculator for Hospitalized Patients with COVID-19. *medRxiv.* 2020.
26. Bhatt AS, Jering KS, Vaduganathan M, et al. Clinical Outcomes in Patients With Heart Failure Hospitalized With COVID-19. *JACC Heart Fail.* 2021;9(1):65-73.
27. Gorodeski EZ, Goyal P, Cox ZL, et al. Virtual Visits for Care of Patients with Heart Failure in the Era of COVID-19: A Statement from the Heart Failure Society of America. *J Card Fail.* 2020;26(6):448-456.
28. Donnelly JP, Wang XQ, Iwashyna TJ, Prescott HC. Readmission and Death After Initial Hospital Discharge Among Patients With COVID-19 in a Large Multihospital System. *JAMA.* 2021;325(3):304-306.
29. Lavery AM, Preston LE, Ko JY, et al. Characteristics of Hospitalized COVID-19 Patients Discharged and Experiencing Same-Hospital Readmission - United States, March-August 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(45):1695-1699.
30. Somani SS, Richter F, Fuster V, et al. Characterization of Patients Who Return to Hospital Following Discharge from Hospitalization for COVID-19. *J Gen Intern Med.* 2020;35(10):2838-2844.



Table 1. Characteristics of patients, admitted to UAB hospital with Covid-19, between March 1 and September 16, 2020

| | Overall sample, n=1024 | No ACEi/ARB Use, n=659 | ACEi/ARB use, n=365 | *P*-value |
|---|---|---|---|---|
| | n, (%) | n, (%) | n, (%) | |
| *Socio-Demographics* | | | | |
| **Age, mean, SD, years** | 57.0 (18.8) | 53.3 (19.7) | 63.7 (14.9) | <0.001 |
| **Age, categories, years** | | | | <0.001 |
| **18-40** | 241 (23.5) | 211 (32.0) | 30 (8.2) | |
| **41-64** | 395 (38.6) | 234 (35.5) | 161 (44.1) | |
| **65-74** | 202 (19.7) | 110 (16.7) | 92 (25.2) | |
| **75 and older** | 186 (18.2) | 104 (15.8) | 82 (22.5) | |
| **Race** | | | | <0.001 |
| **White** | 384 (37.5) | 254 (38.5) | 130 (35.6) | |
| **African American** | 532 (52.0) | 318 (48.3) | 214 (58.6) | |
| **Hispanic or Latino** | 63 (6.2) | 57 (8.6) | 6 (1.6) | |
| **Other** | 20 (2.0) | 12 (1.8) | 8 (2.2) | |
| **Declined to report** | 25 (2.4) | 18 (2.7) | 7 (1.9) | |
| **Male** | 514 (50.2) | 319 (48.4) | 195 (53.4) | 0.12 |
| **Married** | 414 (40.4) | 270 (41.0) | 144 (39.5) | 0.64 |
| **Smoking status** | | | | 0.09 |
| **Never** | 533 (59.6) | 344 (62.3) | 189 (55.1) | |
| **Current** | 98 (10.9) | 58 (10.5) | 40 (11.7) | |
| **Former** | 264 (29.5) | 150 (27.2) | 114 (33.2) | |
| *Comorbidities* | | | | |
| **Body Mass Index (BMI), kg/m2:** | | | | 0.24 |
| **Underweight, BMI < 18.5** | 27 (2.7) | 16 (2.5) | 11 (3.1) | |
| **Normal Weight, BMI=18.5-24** | 227 (22.5) | 159 (24.5) | 68 (18.9) | |
| **Overweight, BMI=25-30** | 268 (26.6) | 168 (25.8) | 100 (27.9) | |
| **Obese, BMI =30 and above** | 487 (48.3) | 307 (47.2) | 180 (50.1) | |
| **Hypertension** | 493 (48.1) | 204 (31.0) | 289 (79.2) | <.001 |
| **Coronary Artery Disease** | 340 (33.2) | 149 (22.6) | 191 (52.3) | <.001 |
| **Diabetes** | 210 (20.5) | 71 (10.8) | 139 (38.1) | <.001 |
| **COPD** | 138 (13.5) | 52 (7.9) | 86 (23.6) | <.001 |
| **Heart Failure** | 323 (31.5) | 131 (19.9) | 192 (52.6) | <.001 |
| **Chronic Kidney Disease** | 325(31.7) | 139(21.1) | 186(51.0) | <.001 |

| | | | | |
|---|---|---|---|---|
| **HIV Positive Status** | 75 (7.3) | 24 (3.6) | 51 (14.0) | <.001 |
| **Sickle Cell Disease** | 10 (1.0) | 7 (1.1) | 3 (0.8) | 0.71 |
| **Recipient of solid organ transplant** | 40 (3.9) | 16 (2.4) | 24 (6.6) | 0.001 |
| *In-hospital Events** | | | | |
| **Admission after July 15, 2020** | 621 (60.6) | 398(60.4) | 223(61.1) | 0.83 |
| **Required Intensive Care Unit** | 466 (45.5) | 287 (43.6) | 179 (49.0) | 0.09 |
| **Invasive mechanical ventilation** | 276 (27.0) | 179 (27.2) | 97 (26.6) | 0.84 |
| **In-hospital Death** | 137(13.4) | 96 (14.6) | 41(11.2) | 0.13 |
| *Post-Discharge events among the survivors of the index admission* | n=877 | n=563 | n=324 | |
| **All-cause same-hospital readmission (during March 1-September 16,2020)** | 170 (19.2) | 97 (16.7) | 76 (23.5) | 0.01 |
| **Death from any cause after index admission** | 16(1.8) | 9(1.0) | 7(2.2) | 0.54 |
| **Cumulative Mortality (death during March 1-September 16,2020)** | 153 (14.9) | 105 (15.9) | 48 (13.2) | 0.23 |

Abbreviations: ACEi – Angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, COPD – chronic obstructive pulmonary disease, HIV – Human Immunodeficiency virus, SBP- systolic blood pressure, SD – standard deviation

Table 2. Factors, associated with in-hospital mortality among patients with Covid-19, admitted to UAB hospital, between March 1 and September 16, 2020. Multivariable-adjusted Cox proportional hazards regression model.

| | aHR | 95% CI | | *P*-value |
|---|---|---|---|---|
| ACEi/ARB Use | 0.56 | 0.36 | 0.88 | 0.01 |
| **Age, years:** | | | | <0.001 |
| **18-40** | ref | - | - | - |
| **40-64** | 1.69 | 0.82 | 3.52 | |
| **65-74** | **4.07** | **2.10** | **9.24** | |
| **75 and older** | **5.53** | **2.52** | **12.14** | |
| **Race:** | | | | 0.55 |
| **African American** | 0.88 | 0.60 | 1.29 | |
| **Hispanic/Latino/Asian/Other** | 0.68 | 0.32 | 1.45 | |
| **White** | ref | | | |
| **Male** | 1.43 | 0.97 | 2.10 | 0.07 |
| **Married** | 0.91 | 0.63 | 1.34 | 0.64 |
| **Current Smoker** | 1.04 | 0.51 | 2.14 | 0.91 |
| **Body Mass Index, kg/m2:** | | | | 0.001 |
| **< 18.5** | 1.91 | 0.63 | 5.79 | |
| **18.5-24** | ref | | | |
| **25-29** | 1.39 | 0.81 | 2.37 | |
| **30 and above** | **2.50** | **1.54** | **4.06** | |
| **Hypertension** | 0.91 | 0.52 | 1.57 | 0.73 |
| **Coronary Artery Disease** | 0.78 | 0.57 | 1.20 | 0.26 |
| **Chronic Kidney Disease** | 0.87 | 0.54 | 1.38 | 0.54 |
| **Heart Failure** | **1.96** | **1.21** | **3.15** | **0.006** |
| **Diabetes** | 1.07 | 0.62 | 1.84 | 0.98 |
| **COPD** | 1.07 | 0.58 | 1.95 | 0.84 |
| **HIV** | 1.51 | 0.76 | 3.03 | 0.23 |
| **Solid organ transplant recipient** | 1.56 | 0.61 | 3.96 | 0.35 |

Abbreviations: ACEi – Angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, CI-confidence interval, COPD – chronic obstructive pulmonary disease, aHR- multivariable-adjusted hazard ratio.

Table 3. Factors associated with same-hospital readmission among patients with Covid-19, between March 1 and September 16, 2020. Multivariable-adjusted Cox proportional hazards regression model. Death after index admission is accounted as a completing risk.

| | aSHR | 95% CI | | p-value |
|---|---|---|---|---|
| **Use of ACEi/ARB** | 1.19 | 0.82 | 1.72 | 0.37 |
| **Age, years:** | | | | 0.23 |
| **18-40** | ref | - | - | - |
| **40-64** | 0.90 | 0.59 | 1.37 | |
| **65-74** | 0.75 | 0.44 | 1.27 | |
| **75 and older** | 0.54 | 0.29 | 1.01 | |
| **Race:** | | | | 0.04 |
| **African American** | 1.11 | 0.78 | 1.60 | |
| **Hispanic/Latino/Asian/Other** | **0.42** | **0.20** | **0.90** | |
| **White** | ref | | | |
| **Male** | 1.01 | 0.71 | 1.43 | 0.95 |
| **Married** | 1.32 | 0.94 | 1.86 | 0.11 |
| **Current Smoker** | 0.70 | 0.40 | 1.20 | 0.19 |
| **Body Mass Index, kg/m2:** | | | | 0.05 |
| **< 18.5** | 1.20 | 0.53 | 2.71 | |
| **18.5-24** | ref | | | |
| **25-29** | 0.69 | 0.44 | 1.07 | |
| **30 and above** | **0.59** | **0.39** | **0.90** | |
| **Hypertension** | 0.84 | 0.51 | 1.38 | 0.48 |
| **Coronary Artery Disease** | 0.87 | 0.58 | 1.29 | 0.47 |
| **Chronic Kidney Disease** | 1.19 | 0.76 | 1.86 | 0.46 |
| **Heart Failure** | 1.41 | 0.92 | 2.16 | 0.11 |
| **Diabetes** | **1.56** | **1.02** | **2.39** | **0.04** |
| **COPD** | 1.28 | 0.76 | 2.14 | 0.36 |
| **HIV** | 0.92 | 0.50 | 1.70 | 0.79 |
| **Solid organ transplant recipient** | 0.84 | 0.39 | 1.81 | 0.66 |

Abbreviations: ACEi – Angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, CI-confidence interval, COPD – chronic obstructive pulmonary disease, aSHR- multivariable-adjusted sub-hazard ratio.

**Bold p-value < .05**

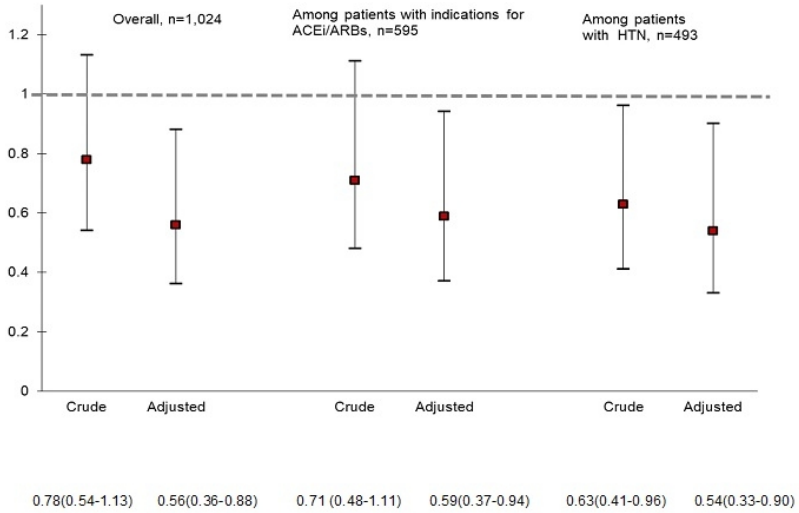


Figure 1. Covid-19 In-Hospital Mortality, Hazard Ratio, 95% Confidence Intervals for ACEi/ARB Use.
Legend. Figure 1 presents crude and adjusted hazards ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

224x153mm (96 x 96 DPI)

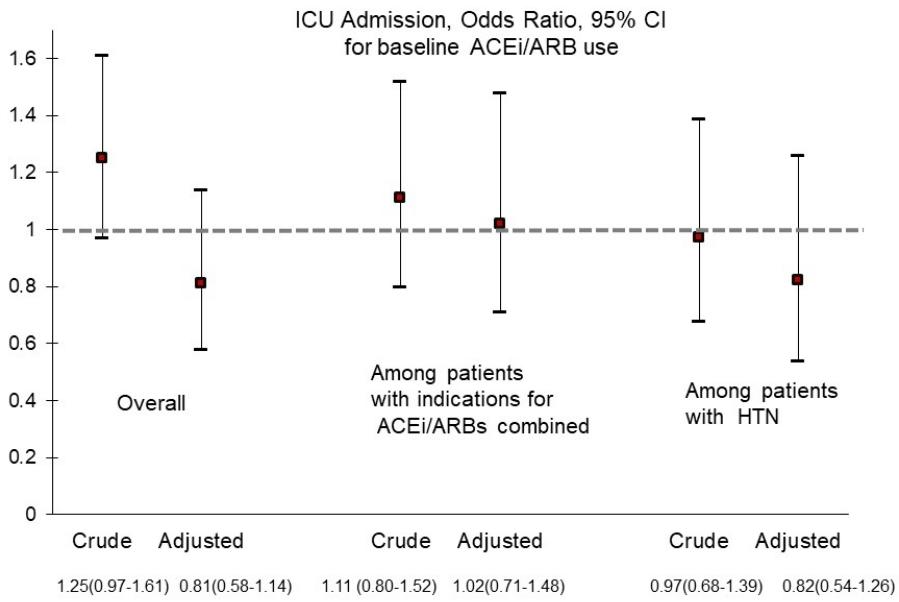


Figure 2. Intensive Care Use, Odds Ratio, 95% CI for ACEi/ARB Use.
Legend: Figure 2 presents crude and adjusted odds ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

254x190mm (96 x 96 DPI)

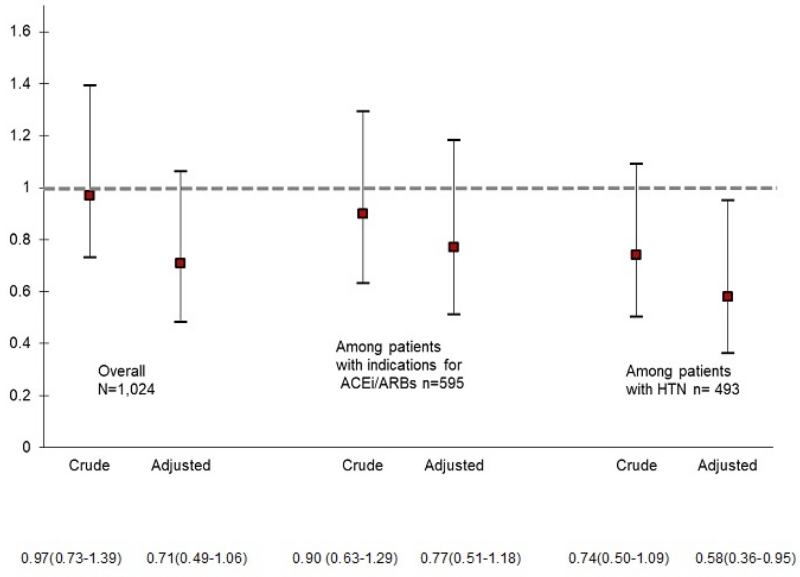


Figure 3. Respiratory Failure, requiring Invasive Mechanical Ventilation, Odd Ratio, 95% Confidence intervals, for ACEi/ARB Use

Legend. Indications for ACEi/ARB use include hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020).

222x145mm (96 x 96 DPI)

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.



| | | Reporting Item | Page Number |
|---|---|---|---|
| **Title and abstract** | | | |
| Title | #1a | Indicate the study's design with a commonly used term in the title or the abstract | 2 |

| | | | |
|---|---|---|---|
| Abstract | #1b | Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background / rationale | #2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | #3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | #4 | Present key elements of study design early in the paper | 4 |
| Setting | #5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 |
| Eligibility criteria | #6a | Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. | 4 |
| Eligibility criteria | #6b | For matched studies, give matching criteria and number of exposed and unexposed | n/a |
| Variables | #7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4 |
| Data sources / measurement | #8 | For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than | 5 |

| | | | |
|---|---|---|---|
| | | one group. Give information separately for for exposed and unexposed groups if applicable. | |
| Bias | #9 | Describe any efforts to address potential sources of bias | 5 |
| Study size | #10 | Explain how the study size was arrived at | 4 |
| Quantitative variables | #11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | 5 |
| Statistical methods | #12a | Describe all statistical methods, including those used to control for confounding | 5 |
| Statistical methods | #12b | Describe any methods used to examine subgroups and interactions | 5 |
| Statistical methods | #12c | Explain how missing data were addressed | 5 |
| Statistical methods | #12d | If applicable, explain how loss to follow-up was addressed | n/a |
| Statistical methods | #12e | Describe any sensitivity analyses | n/a |
| **Results** | | | |
| Participants | #13a | Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed | 6 |

| | | | |
|---|---|---|---|
| | | eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable. | |
| Participants | #13b | Give reasons for non-participation at each stage | n/a |
| Participants | #13c | Consider use of a flow diagram | |
| n/a | | | |
| Descriptive data | #14a | Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable. | 6 |
| Descriptive data | #14b | Indicate number of participants with missing data for each variable of interest | |
| 6 | | | |
| Descriptive data | #14c | Summarise follow-up time (eg, average and total amount) | |
| 7 | | | |
| Outcome data | #15 | Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable. | |
| 7 | | | |

| | | | |
|---|---|---|---|
| Main results | #16a | Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 7,8 |
| Main results | #16b | Report category boundaries when continuous variables were categorized | 6 |
| Main results | #16c | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| n/a | | | |
| Other analyses | #17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 7,8 |
| **Discussion** | | | |
| Key results | #18 | Summarise key results with reference to study objectives | 8 |
| Limitations | #19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. | 9 |
| Interpretation | #20 | Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. | 9 |
| Generalisability | #21 | Discuss the generalisability (external validity) of the study results | 10 |
| **Other Information** | | | |

| | | | |
|---|---|---|---|
| Funding | #22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 11 |

BMJ Open

# What is the Association of Renin-Angiotensin-Aldosterone System Inhibitors with Covid-19 Outcomes: Retrospective Study of Racially Diverse Patients?



| | |
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# What is the Association of Renin-Angiotensin-Aldosterone System Inhibitors with Covid-19 Outcomes: Retrospective Study of Racially Diverse Patients?

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**Abstract.**

**Objective:** To describe the clinical outcomes of Covid-19 in a racially diverse sample from the US Southeast and examine the association of renin-angiotensin-aldosterone system (RAAS) inhibitor use with Covid-19 outcome.

**Design, Setting, Participants:** This study is a retrospective cohort of 1,024 patients with reverse-transcriptase–polymerase-chain-reaction-confirmed Covid-19 infection, admitted to a 1,242-bed teaching hospital in Alabama. Data on RAAS inhibitors use, demographics and comorbidities were extracted from hospital medical records.

**Primary Outcome**s: In-hospital mortality, a need of intensive care (ICU), respiratory failure, defined as invasive mechanical ventilation (iMV), and 90-day same-hospital readmissions.

**Results:** Among 1024 patients (mean [SD] age, 57 [18.8] years), 532 [52.0%] were African Americans, 514 [50.2%] male, 493 [48.1%] had hypertension, 365 [36%] were taking RAAS inhibitors. During index hospitalization (median length of stay of 7 (interquartile range [4-15]) days) 137(13.4%) patients died; 170(19.2%) of survivors were re-admitted. RAAS inhibitor use was associated with lower in-hospital mortality (adjusted hazard ratio, 95%CI [0.56, (0.36-0.88), *P*=0.01) and no effect modification by race was observed (*P* for interaction = 0.81). Among patients with hypertension, baseline RAAS use was associated with reduced risk of iMV, adjusted odds ratio, 95% CI [aOR=0.58, 95%CI (0.36-0.95), *P*=0.03]. Patients with heart failure were twice as likely to die from Covid-19, compared to patients without heart failure.

**Conclusions:** In a retrospespective study of racially diverse patients, hospitalized with Covid-19, pre-hospitalization use of RAAS inhibitors was associated with 40% reduction in mortality irrespective of race.

**Article summary.**

**Strength and limitations.**

- This study background was based on multiple questions on RAAS safety, raised by the community of the primary care physicians and patients in the beginning of the COVID-19 pandemic.
- Other strengths of the study include a large racially diverse sample of patients with COVID-19 from the US Southeast and a robust approach to extraction of data from electronic health records.
- Observational retrospective nature of this study does not allow drawing causal inferences.
- Residual unmeasured confounding, such as socio-ecomonic status, may influence study results.
- The study included patients from a limited geographical area and a single hospital site.
- The data on out- of-hospital mortality and same-hospital readmissions may be incomplete as some Covid-19 patients may have been readmitted to other area hospitals.

**Introduction.**

The United States has experienced an unprecedented public health crisis with the Covid-19 pandemic.[1] Persons with cardiovascular and metabolic disease are at increased risk for mortality and morbidity from Covid-19[2-5]. Cardiovascular disease and diabetes mellitus are highly prevalent among US adults, with 45% of adults having HTN, 13% - diabetes mellitus, 6.7% - coronary artery disease, and 2.4% - heart failure[6]. These chronic conditions disproportionally affect adults in the Southeast compared to other parts of the US[6]. Patients with hypertension, heart failure, diabetes, and chronic kidney disease are often prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors, i.e., angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). In animal studies, performed prior to the emergence of Covid-19, ACEi were found to increase the expression of ACE2 receptors.[7] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to ACE2 receptors in lungs[8], leading to concerns about potential risks of utilizing RAAS inhibitors in the setting of Covid-19. While subsequent studies have demonstrated the safety of RAAS inhibitor use among persons with Covid-19 and indication for RAAS use[9-11], the association of RAAS inhibitor use with hospital readmission after the index Covid-19 admission is not well described.

Most of reports[12] describing the associations of pre-existing use of RAAS inhibitors with COVID-19 outcomes were obtained in White or Asian, not African American populations. Compared to Whites, African Americans have a high incidence of adverse effects of RAAS inhibitors [13]. Disproportionally affected by multiple health disparities, African Americans have also been shown to have an increased risk of severe COVID-19, requiring hospitalization[14]. Persons of African descent were also at higher risk of contracting COVID-19 in the largest to date cohort study of the Covid-19 susceptibility in England[15].

To better understand the association of baseline RAAS inhibitor use with outcomes of Covid-19 hospitalization, we assembled an observational retrospective cohort of racially diverse hospitalized patients with laboratory-confirmed Covid-19 in Alabama. We examined whether baseline RAAS inhibitor use was associated with Covid-19 health outcomes, including 1) in-hospital mortality, 2) need for Intensive Care Unit (ICU)

admission 3) acute respiratory failure requiring intubation and mechanical ventilation (iMV), and 4) same-hospital readmission for any cause among survivors of the Covid-19 index hospitalization. We also assessed whether the association between RAAS inhibitor use and mortality differed by race.

**Methods.**

**Study participants and procedures.**

This observational retrospective cohort study included 1024 adult (age 18 and above) patients hospitalized with confirmed Covid-19 between March 1 and September 16, 2020 at the University of Alabama at Birmingham (UAB) teaching hospital in Birmingham, Alabama. The first cases of the Covid-19 were detected in Birmingham beginning on March 1, 2020. The cases increased very slowly over the spring of 2020, with a sharp surge 10-14 days after July 4, 2020. After the initial surge, Covid-19 cases declined slightly in August 2020, but then started to rise, achieving an spike in December-January 2021 (data not included in this report). The UAB ICU neared but did not exceed capacity. During the first surge of Covid-19 cases in July 2020, UAB Hospital implemented a delayed intubation strategy, favoring treating Covid-19 respiratory failure with supplemental oxygen, delivered via high flow nasal cannula. Therefore, all analyses of respiratory failure were adjusted for the time of the index admission for Covid-19 (before vs. after July 15, 2020).

Covid-19 cases were confirmed by reverse-transcriptase polymerase chain-reaction testing (rt-PCR). We extracted patient data electronically from our institution's Electronic Health Record (EHR; Cerner) data warehouse (i2B2) supplemented by manual chart review. Data were prepared for analyses by the COVID Core data Extraction/Transformation team using Oracle SQL developer (v.11.2). For each of the patients with lab-confirmed Covid-19, encounter data for the index admission were obtained, including admission date, date of the earliest positive rt-PCR for Covid-19 and death or discharge date. The admission/discharge dates for all subsequent outpatient and inpatient encounters and dates of death after the index hospitalization were also electronically extracted. For each of the hospital readmissions (n=172) a manual chart review was conducted to confirm admission/discharge dates. For each of the deaths (n=16) that occurred after index hospitalization we conducted manual chart review for confirmation. From the initial sample of 1029 patients, we excluded 5

patients with missing index admission dates or missing dates of birth. The study procedures were approved by the UAB Institutional Review Board.

**Patient and public Involvement.**

No patient involved.

**Outcomes and main exposure.**

Study outcomes included in-hospital Covid-19-related mortality, need for the ICU admission, respiratory failure defined by a need for invasive mechanical ventilation, and same-hospital readmission for any cause after the index hospitalization. Data on RAAS inhibitors included use of ACEis and ARBs prior to the index Covid-19 hospitalization, and were derived from the index admission medication reconciliation data in the EHR. If patients were taking a combination medicine that included an ACEi or ARB as one of the components, they were classified as having been prescribed ACEi/ARB in the analysis.

**Covariates.**

Covariates were selected on the basis of the risk factors for severe Covid-19 infection identified by the Centers for Disease Control and Prevention and previous reports on Covid-19 morbidity and mortality [16-19]. Patient socio-demographic characteristics included age at the index admission (calculated, using birth and admission dates) and self-reported race, sex, marital status, and cigarette smoking status. We created age categories as follows: 18-40, 41-64, 65-74, and 75 years and older. Body mass index (BMI) was calculated using height and weight obtained most recently prior to the index Covid-19 admission. BMI categories included: "underweight" is less than 18.5 kg/m$^2$, "normal weight" 18.5-24.9 kg/m$^2$, "overweight" 25-29.9 kg/m$^2$ and "obese" 30 kg/m$^2$,and above. We obtained data on comorbidities, including hypertension, coronary artery disease, diabetes, chronic obstructive pulmonary disease (COPD), heart failure, chronic kidney disease, HIV, sickle cell disease, and history of solid organ transplant using corresponding ICD-10 codes.

**Statistical Analysis.**

Patients with Covid-19 who were prescribed RAAS inhibitors at baseline were compared to those who were not prescribed RAAS inhibitors using two-sided t-tests for continuous variables and Chi-square tests for

categorical variables. We examined the association of RAAS inhibitor use with study outcomes in three different samples: 1) overall sample, 2) patients with any indication for RAAS inhibitor use, such as hypertension, diabetes, chronic kidney disease, coronary artery disease or heart failure and 3) patients with hypertension. Outcomes were assessed with unadjusted and multivariable models. To examine the association of in-hospital mortality from Covid-19 with baseline RAAS inhibitor use we constructed Cox proportional hazards regression models adjusted for age, sex, race, marital status, smoking, BMI, and medical conditions. We created an interaction term between RAAS use and race to test for effect modification by race in the fully adjusted models of Covid-19 in-hospital mortality. The need for ICU and the presence of respiratory failure were examined separately in logistic regression models, with adjustment for the same patient characteristics and for the time of admission (before vs. after July 15, 2020).

We examined the charts of the survivors of the index Covid-19 admission post-discharge for a same-hospital readmission for any cause using medical records. The EHR data were abstracted for any subsequent in-hospital and outpatient encounter after the index hospitalization and UAB hospital readmission dates were extracted. The time to readmission was calculated using index discharge data and readmission date. To examine the association between baseline RAAS use and readmissions, we used the Fine and Gray Model to account for competing risk of death in the post-discharge period that was adjusted for the same patient characteristics. The proportionality assumption was tested and satisfied in the Cox proportion hazards models. All statistical analyses were performed in SAS software (SAS Institute, Cary, NC) version 9.4,

**Results.**

Among 1024 patients, admitted to UAB hospital with Covid-19 (mean [SD] age, 57 [18.8] years), 532 [52%] were African American, 514 [50 %] were male, 493 [48 %] had hypertension, 323 [32 %] had heart failure, 487 [48 %] were obese, 210 [20.5%] had diabetes and 98 [11 %] were current smokers (Table 1). There were 365 [36%] patients taking RAAS inhibitors at baseline. Patients with baseline RAAS use were older, more likely to be African American, and had more comorbidities.

The median length of stay (LOS) for the index Covid-19 hospitalization was 7 days, [interquartile range (IQR) 4-15 days]. Maximum LOS was 175 days. Sixty percent of included Covid-19 cases were admitted after the initial surge in Birmingham, between July 15 and September 16, 2020. During the index hospitalization, 137 (13.4%) patients died. Additionally, 16 (1.8%) patients died from any cause post-discharge, either during a hospital readmission or out of the hospital. Cumulative all-cause mortality included 153 (14.9%) deaths. At the time of the cohort assembly on September 16, 2020, 23 patients remained in the hospital. During the index hospitalization 466 (45.5%) patients required ICU care, and 276 (27%) persons required iMV. The proportion of patients who were intubated was higher in the early period, before July 15, compared to the period of after July 15,2020, when placing the patient with respiratory failure on high flow nasal canula became a preferred treatment strategy: 201 [32.4%] vs. 75 [ 18.6], *P* <.001.

**In-hospital Covid-19 mortality and RAAS use.**

The median time to death was 13 days [IQR 6-20 days]. In the overall study sample, baseline RAAS inhibitor use was associated with significantly reduced risk of in-hospital mortality (adjusted hazard ratio [aHR] 0.56, 95% confidence interval [95%CI] 0.36-0.88], *P*=0.01, after adjustment for all covariates) (Figure 1). A similar protective effect of RAAS inhibitor use on mortality was observed among patients with any indication for RAAS inhibitor use (aHR [95%CI] for RAAS inhibitor use 0.59, 95%CI 0.37-0.94, *P*=0.03) and among patients with hypertension (aHR for RAAS use 0.54, 95%CI 0.33-0.90, *P*=0.02). We did not observe effect modification by race in the overall sample. The RAAS inhibitor use*race interaction term had associated *P*= 0.81. Compared to Whites, African American race was not associated with in-hospital mortality from Covid-19 in the adjusted model (aHR 0.88, 95% CI 0.60-1.29, *P* for trend 0.55) (Table 2). Other factors associated with increased cumulative mortality in our sample included age 65-74 years (aHR 3.67 [95%CI 1.85-7.31]), age 75 years and older (aHR 4.89 [95%CI 2.36-10.14]), obesity (aHR 2.10 [95%CI 1.34-3.29]), and pre-existing heart failure (aHR 1.88 [95%CI 1.20-2.94]) (Table 2).

**Covid-19 in-hospital events and RAAS inhibitor use.**

RAAS inhibitor use was not associated with the need for ICU in all analyses (Figure 2.) In the overall patient sample, RAAS use was not associated with iMV, aOR 0.71[95%CI 0.48-1.06] (Figure 3). In contrast, among patients with hypertension, baseline RAAS inhibitor use was significantly associated with reduced odds of iMV after adjustment for covariates (aOR 0.58 [95%CI 0.36-0.95], *P*=.03). African Americans admitted with Covid-19 were more likely to have respiratory failure, requiring iMV: aOR 1.58 [95%CI 1.01-2.31], *P*=.02. Other factors associated with the increased risk of iMV for the Covid-19-related respiratory failure included current cigarette smoking (aOR 1.80 [95%CI 1.08-3.02], *P*=.03), pre-existing heart failure (aOR 2.32 [95%CI 1.45-3.71], *P* <.001) and being admitted to UAB before July 15, 2020 (aOR 1.97 [95%CI 1.39-2.79], *P* <.0010.

**Same-hospital 90-day readmissions among Covid-19 survivors.**

Over a median follow up of 51 [IQR 28-82] days, 170 (19.2%) of 887 discharged patients were readmitted to the same hospital for any cause (Table 1). Among those who were re-hospitalized, the median time to readmission following the index discharge was 10 days [IQR 4-29 days]. The proportion of persons with same-hospital readmission among those with baseline RAAS inhibitor use was 23.5%, compared to 16.7% among those who were not prescribed RAAS inhibitors *(P*=0.01) (Table 1). In the fully adjusted Cox proportional models, accounting for death as a competing risk, baseline RAAS agent use was not associated with readmissions (Table 3). Compared to White patients, patients of the Hispanic/Latino/Asian or other race/ethnicity were less likely to be readmitted (aHR 0.42, 95% CI 0.20-0.90). African-American race was not statistically significantly associated with hospital readmission (aHR 1.11, 95% CI 0.78-1.60). Among the chronic medical conditions only diabetes was significantly associated with higher risk for same-hospital readmission after the index Covid-19 admission (aHR 1.56, 95%CI 1.02-2.94).

**Discussion.**

This study presents data from 1024 patients with Covid-19 admitted to a teaching hospital in Alabama. Results of this study support the safety of maintaining patients with chronic conditions on ACEis and ARBs during the Covid-19 pandemic and expands previous reports by demonstrating the protective effect of the ACEis/ARBs from mortality in a racially diverse sample of patients with Covid-19. Among patients with

hypertension, the use of ACEis/ARsB prior to contracting Covid-19 was associated with a reduction in the likelihood of endotracheal intubation by nearly 40%. Further, ACEi/ARB use was not associated with greater need for ICU–level care or with an increase in the same-hospital readmissions.

Baseline use of ACEi/ARB was associated with 40% lower in-hospital mortality in patients with Covid-19, after controlling for potential confounders such as age, sex, race, obesity, smoking, and chronic medical conditions. These results were similar in the sample of patients who had any indication for RAAS inhibitors, and in patients with hypertension. Previous research has shown no association between the use of RAAS inhibitors and susceptibility to Covid-19,[20] and has demonstrated the safety of continuing these medications during the pandemic[10,11,21]. Similary to our results, in 1.4 million patients with hypertension, heart failure, diabetes, kidney disease, or ischemic heart disease registered in the Swedish National Patient Registry, ACEi/ARB use was associated with a reduced mortality in Covid-19 cases (aHR 0.89, 95% CI [0.82-0.96])[22]. Our study expands on previous findings by demonstrating both safety and reduction in Covid-19-related mortality associated with RAAS inhibitor use in a racially diverse sample where 50% of patients were African American. Potential mechanisms of protective effects of ACEi/ARB in Covid-19 are not well understood. One of the potential explanations of the decreased mortality among patients on ACEi/ARB medications prior to Covid-19 is that patients' chronic conditions were better controlled before the infection, which, in turn, reduced complications of Covid-19. Another body of research suggests that prolonged RAAS use may, in fact, downregulate ACE2 receptor expression, limit inflammation and reduce lung injury in Covid-19[23-25]. Unfortunately, the design of our study does not allow us to prove or disapprove this hypothesis.

Half of the patients hospitalized with the Covid-19 infection in our sample were African American, whereas the proportion of African Americans in Alabama is only 26.7%. This finding highlights the racial disparity in the Covid-19 pandemic, in which a higher proportion of African Americans developed severe Covid-19 infection, requiring hospitalization[26], compared to Whites. African Americans were also more likely to require iMV in our study. However, similar to other studies of Covid-19 outcomes in the US[27], race was not an independent predictor of death or hospital readmission in our study.

Our findings confirm previous observations that advanced age, obesity, and comorbidities are associated with death from Covid-19 [16,28]. Importantly, more than 30% of our patient sample admitted with severe Covid-19 had pre-existing heart failure, a rate almost ten times higher than the prevalence of heart failure in the general population. Heart failure was the only chronic condition, in addition to age and obesity in our sample, that was independently associated with increased in-hospital mortality from complications related to Covid-19. Patients with heart failure were also at increased risk of developing respiratory failure, requiring iMV. These represent a particularly vulnerable group requiring special attention from healthcare to reduce mortality and morbidity from the Covid-19[29 30].

The rate of same-hospital readmissions among Covid-19 survivors was 19%, similar to that in a recent study of the patients with Covid-19, treated in the Veterans Affairs hospital system[31] but higher, than in other reports estimating that only 3-10% of patients were re-hospitalized after the index Covid-19 admission[32,33]. The high rates of hospital readmission in our study sample may be explained by the high level of chronic disease prevalence and worse general health in the general population of Alabama. Importantly, diabetes was significantly associated with increased re-admission risk among Covid-19 survivors. Alabama has the third highest prevalence of diabetes among adults (14%) in the United States, according to the National Diabetes Statistics Report-2020 by the Centers of Disease Control. Our findings are likely to extend to states with a similar high prevalence of diabetes mellitus and underscore the importance of close outpatient follow-up of this at risk population.

Study limitations include limited geographical area and single hospital site. The data on out- of-hospital mortality and same-hospital readmissions may be incomplete, as some Covid-19 patients may have been readmitted to other area hospitals. On average 30% of patients originally admitted to the UAB hospital are re-admitted to other hospitals. The observational retrospective nature of this study does not allow drawing causal inferences. Additionally, residual unmeasured confounding, such as socio-ecomonic status, may influence study results. EHR data regarding pre-existing medical conditions and smoking may be incomplete. Strengths of the study include a large racially diverse sample from the US Southeast, a region disproportionally affected by

Covid-19 and high prevalence of multiple comorbidities. Further, we were able to develop a robust approach to extraction of data from EHR and assemble a cohort of the patients with Covid-19.

In conclusion, in this retrospective study the use of RAAS inhibitors was associated with decreased in-hospital mortality from Covid-19 in a racially diverse sample. RAAS inhibitor use was not associated with ICU-level care or hospital readmissions in the cohort of patients with Covid-19, while patients with diabetes were at a high risk for same-hospital readmission. Among patients with hypertension, baseline RAAS inhibitor use was associated with a reduced risk of invasive mechanical ventilation. This retrospective study may support the continuation of RAAS inhibitors during the Covid-19 pandemic unless there are contraindications for these pharmacological agents.

**Data availability statement.**

All data relevant to the study are available from the corresponding author on request.

**Ethics statements.**

The study procedures were approved by the UAB Institutional Review Board.

***Patient consent for publication:***

Not required.

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**Authors statement.**

YK delineated project idea and design, conducted data analysis and drafted the manuscript.

YK, GM conducted data management and analysis.

YK, GM, JW had full access to data and ensured the accuracy or integrity of data.

SC, RF, MS, PG, SO, AC, EAJ edited and revised the manuscript.

All authors provided substantial contributions to the conception or design of the work; interpretation of data; revising the draft critically for important intellectual content; and final approval of the version to be published.

**Conflicts of interest.**

Dr. Cherrington reports serving as a consultant for Bayer. Dr Jackson reports research funding from NIH, and Amgen; editorial board membership: Circulation: Cardiovascular Quality and Outcomes; consulting: American College of Cardiology and McKesson, Inc.; Expert witness for DeBlase Brown Everly LLP.; and royalties for UpToDate. Dr. Safford reports research funding from Amgen. Dr. Oparil reports research funding from Bayer, CinCor Pharma Inc, George Medicine Pty Limited and Idorsia Pharmaceuticals. Other authors report no conflict of interest.

**Figure Legends.**

**Figure 1. Covid-19 In-Hospital Mortality, Hazard Ratio, 95% Confidence Intervals for ACEi/ARB Use.**

Legend. Figure 1 presents crude and adjusted hazards ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

**Figure 2. Intensive Care Use, Odds Ratio, 95% CI for ACEi/ARB Use.**

Legend: Figure 2 presents crude and adjusted odds ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

**Figure 3. Respiratory Failure, requiring Invasive Mechanical Ventilation, Odd Ratio, 95% Confidence intervals, for ACEi/ARB Use**

Legend. Indications for ACEi/ARB use include hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020).

**References:**


1. Fauci AS, Lane HC, Redfield RR. Covid-19 - Navigating the Uncharted. *N Engl J Med.* 2020;382(13):1268-1269.
2. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol.* 2020.
3. Porcheddu R, Serra C, Kelvin D, Kelvin N, Rubino S. Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. *J Infect Dev Ctries.* 2020;14(2):125-128.
4. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis.* 2020.
5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.
6. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation.* 2020;141(9):e139-e596.
7. Vuille-dit-Bille RN, Camargo SM, Emmenegger L, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. *Amino Acids.* 2015;47(4):693-705.
8. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *J Virol.* 2020;94(7).
9. Mackey K, King VJ, Gurley S, et al. Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults: A Living Systematic Review. *Ann Intern Med.* 2020;173(3):195-203.
10. Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med.* 2021.
11. Fosbol EL, Butt JH, Ostergaard L, et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. *JAMA.* 2020;324(2):168-177.
12. Shah P, Owens J, Franklin J, Jani Y, Kumar A, Doshi R. Baseline use of angiotensin-converting enzyme inhibitor/AT1 blocker and outcomes in hospitalized coronavirus disease 2019 African-American patients. *J Hypertens.* 2020;38(12):2537-2541.
13. Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension.* 2008;51(6):1624-1630.

14. Gu T, Mack JA, Salvatore M, et al. Characteristics Associated With Racial/Ethnic Disparities in COVID-19 Outcomes in an Academic Health Care System. *JAMA Netw Open.* 2020;3(10):e2025197.
15. Hippisley-Cox J, Young D, Coupland C, et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart.* 2020;106(19):1503-1511.
16. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA.* 2020;323(20):2052-2059.
17. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ.* 2020;371:m3731.
18. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical Characteristics of Covid-19 in New York City. *N Engl J Med.* 2020;382(24):2372-2374.
19. Goyal P, Ringel JB, Rajan M, et al. Obesity and COVID-19 in New York City: A Retrospective Cohort Study. *Ann Intern Med.* 2020;173(10):855-858.
20. Mehta N, Kalra A, Nowacki AS, et al. Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(9):1020-1026.
21. Lopes RD, Macedo AVS, de Barros ESPGM, et al. Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial. *JAMA.* 2021;325(3):254-264.
22. Savarese G, Benson L, Sundstrom J, Lund LH. Association between renin-angiotensin-aldosterone system inhibitor use and COVID-19 hospitalization and death: a 1.4 million patient nationwide registry analysis. *Eur J Heart Fail.* 2021;23(3):476-485.
23. Baral R, Tsampasian V, Debski M, et al. Association Between Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis. *JAMA Netw Open.* 2021;4(3):e213594.
24. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med.* 2020;382(25):2441-2448.
25. Zhang P, Zhu L, Cai J, et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19. *Circ Res.* 2020;126(12):1671-1681.
26. Chang MH, Moonesinghe R, Truman BI. COVID-19 Hospitalization by Race and Ethnicity: Association with Chronic Conditions Among Medicare Beneficiaries, January 1-September 30, 2020. *J Racial Ethn Health Disparities.* 2021.
27. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. *N Engl J Med.* 2020;382(26):2534-2543.
28. Levy TJ, Richardson S, Coppa K, et al. Development and Validation of a Survival Calculator for Hospitalized Patients with COVID-19. *medRxiv.* 2020.
29. Bhatt AS, Jering KS, Vaduganathan M, et al. Clinical Outcomes in Patients With Heart Failure Hospitalized With COVID-19. *JACC Heart Fail.* 2021;9(1):65-73.
30. Gorodeski EZ, Goyal P, Cox ZL, et al. Virtual Visits for Care of Patients with Heart Failure in the Era of COVID-19: A Statement from the Heart Failure Society of America. *J Card Fail.* 2020;26(6):448-456.
31. Donnelly JP, Wang XQ, Iwashyna TJ, Prescott HC. Readmission and Death After Initial Hospital Discharge Among Patients With COVID-19 in a Large Multihospital System. *JAMA.* 2021;325(3):304-306.
32. Lavery AM, Preston LE, Ko JY, et al. Characteristics of Hospitalized COVID-19 Patients Discharged and Experiencing Same-Hospital Readmission - United States, March-August 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(45):1695-1699.
33. Somani SS, Richter F, Fuster V, et al. Characterization of Patients Who Return to Hospital Following Discharge from Hospitalization for COVID-19. *J Gen Intern Med.* 2020;35(10):2838-2844.

Table 1. Characteristics of patients, admitted to UAB hospital with Covid-19, between March 1 and September 16, 2020

| | Overall sample, n=1024 | No ACEi/ARB Use, n=659 | ACEi/ARB use, n=365 | *P*-value |
|---|---|---|---|---|
| | n, (%) | n, (%) | n, (%) | |
| *Socio-Demographics* | | | | |
| **Age, mean, SD, years** | 57.0 (18.8) | 53.3 (19.7) | 63.7 (14.9) | <0.001 |
| **Age, categories, years** | | | | <0.001 |
| **18-40** | 241 (23.5) | 211 (32.0) | 30 (8.2) | |
| **41-64** | 395 (38.6) | 234 (35.5) | 161 (44.1) | |
| **65-74** | 202 (19.7) | 110 (16.7) | 92 (25.2) | |
| **75 and older** | 186 (18.2) | 104 (15.8) | 82 (22.5) | |
| **Race** | | | | <0.001 |
| **White** | 384 (37.5) | 254 (38.5) | 130 (35.6) | |
| **African American** | 532 (52.0) | 318 (48.3) | 214 (58.6) | |
| **Hispanic or Latino** | 63 (6.2) | 57 (8.6) | 6 (1.6) | |
| **Other** | 20 (2.0) | 12 (1.8) | 8 (2.2) | |
| **Declined to report** | 25 (2.4) | 18 (2.7) | 7 (1.9) | |
| **Male** | 514 (50.2) | 319 (48.4) | 195 (53.4) | 0.12 |

| | | | | |
|---|---|---|---|---|
| **Married** | 414 (40.4) | 270 (41.0) | 144 (39.5) | 0.64 |
| **Smoking status** | | | | 0.09 |
| **Never** | 533 (59.6) | 344 (62.3) | 189 (55.1) | |
| **Current** | 98 (10.9) | 58 (10.5) | 40 (11.7) | |
| **Former** | 264 (29.5) | 150 (27.2) | 114 (33.2) | |
| *Comorbidities* | | | | |
| **Body Mass Index (BMI), kg/m2:** | | | | 0.24 |
| **Underweight, BMI < 18.5** | 27 (2.7) | 16 (2.5) | 11 (3.1) | |
| **Normal Weight, BMI=18.5-24** | 227 (22.5) | 159 (24.5) | 68 (18.9) | |
| **Overweight, BMI=25-30** | 268 (26.6) | 168 (25.8) | 100 (27.9) | |
| **Obese, BMI =30 and above** | 487 (48.3) | 307 (47.2) | 180 (50.1) | |
| **Hypertension** | 493 (48.1) | 204 (31.0) | 289 (79.2) | <.001 |
| **Coronary Artery Disease** | 340 (33.2) | 149 (22.6) | 191 (52.3) | <.001 |
| **Diabetes** | 210 (20.5) | 71 (10.8) | 139 (38.1) | <.001 |
| **COPD** | 138 (13.5) | 52 (7.9) | 86 (23.6) | <.001 |
| **Heart Failure** | 323 (31.5) | 131 (19.9) | 192 (52.6) | <.001 |
| **Chronic Kidney Disease** | 325(31.7) | 139(21.1) | 186(51.0) | <.001 |
| **HIV Positive Status** | 75 (7.3) | 24 (3.6) | 51 (14.0) | <.001 |
| **Sickle Cell Disease** | 10 (1.0) | 7 (1.1) | 3 (0.8) | 0.71 |
| **Recipient of solid organ transplant** | 40 (3.9) | 16 (2.4) | 24 (6.6) | 0.001 |
| *In-hospital Events** | | | | |
| **Admission after July 15, 2020** | 621 (60.6) | 398(60.4) | 223(61.1) | 0.83 |
| **Required Intensive Care Unit** | 466 (45.5) | 287 (43.6) | 179 (49.0) | 0.09 |
| **Invasive mechanical ventilation** | 276 (27.0) | 179 (27.2) | 97 (26.6) | 0.84 |
| **In-hospital Death** | 137(13.4) | 96 (14.6) | 41(11.2) | 0.13 |
| *Post-Discharge events among the survivors of the index admission* | n=877 | n=563 | n=324 | |
| **All-cause same-hospital readmission (during March 1-September 16,2020)** | 170 (19.2) | 97 (16.7) | 76 (23.5) | 0.01 |
| **Death from any cause after index admission** | 16(1.8) | 9(1.0) | 7(2.2) | 0.54 |
| **Cumulative Mortality (death during March 1-September 16,2020)** | 153 (14.9) | 105 (15.9) | 48 (13.2) | 0.23 |

Abbreviations: ACEi – Angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, COPD – chronic obstructive pulmonary disease, HIV – Human Immunodeficiency virus, SBP- systolic blood pressure, SD – standard deviation



Table 2. Factors, associated with in-hospital mortality among patients with Covid-19, admitted to UAB hospital, between March 1 and September 16, 2020. Multivariable-adjusted Cox proportional hazards regression model.

| | **aHR** | **95% CI** | | ***P*-value** |
|---|---|---|---|---|
| ACEi/ARB Use | 0.56 | 0.36 | 0.88 | 0.01 |
| **Age, years:** | | | | <0.001 |
| **18-40** | ref | - | - | - |
| **40-64** | 1.69 | 0.82 | 3.52 | |
| **65-74** | **4.07** | **2.10** | **9.24** | |
| **75 and older** | **5.53** | **2.52** | **12.14** | |
| **Race:** | | | | 0.55 |
| **African American** | 0.88 | 0.60 | 1.29 | |
| **Hispanic/Latino/Asian/Other** | 0.68 | 0.32 | 1.45 | |
| **White** | ref | | | |
| **Male** | 1.43 | 0.97 | 2.10 | 0.07 |
| **Married** | 0.91 | 0.63 | 1.34 | 0.64 |
| **Current Smoker** | 1.04 | 0.51 | 2.14 | 0.91 |

| | | | | |
|---|---|---|---|---|
| **Body Mass Index, kg/m2:** | | | | 0.001 |
| **< 18.5** | 1.91 | 0.63 | 5.79 | |
| **18.5-24** | ref | | | |
| **25-29** | 1.39 | 0.81 | 2.37 | |
| **30 and above** | **2.50** | **1.54** | **4.06** | |
| **Hypertension** | 0.91 | 0.52 | 1.57 | 0.73 |
| **Coronary Artery Disease** | 0.78 | 0.57 | 1.20 | 0.26 |
| **Chronic Kidney Disease** | 0.87 | 0.54 | 1.38 | 0.54 |
| **Heart Failure** | **1.96** | **1.21** | **3.15** | **0.006** |
| **Diabetes** | 1.07 | 0.62 | 1.84 | 0.98 |
| **COPD** | 1.07 | 0.58 | 1.95 | 0.84 |
| **HIV** | 1.51 | 0.76 | 3.03 | 0.23 |
| **Solid organ transplant recipient** | 1.56 | 0.61 | 3.96 | 0.35 |

Abbreviations: ACEi – Angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, CI-confidence interval, COPD – chronic obstructive pulmonary disease, aHR- multivariable-adjusted hazard ratio.

Table 3. Factors associated with same-hospital readmission among patients with Covid-19, between March 1 and September 16, 2020. Multivariable-adjusted Cox proportional hazards regression model. Death after index admission is accounted as a completing risk.

| | **aSHR** | **95% CI** | | **p-value** |
|---|---|---|---|---|
| **Use of ACEi/ARB** | 1.19 | 0.82 | 1.72 | 0.37 |
| **Age, years:** | | | | 0.23 |
| **18-40** | ref | - | - | - |
| **40-64** | 0.90 | 0.59 | 1.37 | |
| **65-74** | 0.75 | 0.44 | 1.27 | |
| **75 and older** | 0.54 | 0.29 | 1.01 | |
| **Race:** | | | | 0.04 |
| **African American** | 1.11 | 0.78 | 1.60 | |
| **Hispanic/Latino/Asian/Other** | **0.42** | **0.20** | **0.90** | |
| **White** | ref | | | |
| **Male** | 1.01 | 0.71 | 1.43 | 0.95 |
| **Married** | 1.32 | 0.94 | 1.86 | 0.11 |
| **Current Smoker** | 0.70 | 0.40 | 1.20 | 0.19 |

| | | | | |
|---|---|---|---|---|
| **Body Mass Index, kg/m2:** | | | | 0.05 |
| **< 18.5** | 1.20 | 0.53 | 2.71 | |
| **18.5-24** | ref | | | |
| **25-29** | 0.69 | 0.44 | 1.07 | |
| **30 and above** | **0.59** | **0.39** | **0.90** | |
| **Hypertension** | 0.84 | 0.51 | 1.38 | 0.48 |
| **Coronary Artery Disease** | 0.87 | 0.58 | 1.29 | 0.47 |
| **Chronic Kidney Disease** | 1.19 | 0.76 | 1.86 | 0.46 |
| **Heart Failure** | 1.41 | 0.92 | 2.16 | 0.11 |
| **Diabetes** | **1.56** | **1.02** | **2.39** | **0.04** |
| **COPD** | 1.28 | 0.76 | 2.14 | 0.36 |
| **HIV** | 0.92 | 0.50 | 1.70 | 0.79 |
| **Solid organ transplant recipient** | 0.84 | 0.39 | 1.81 | 0.66 |

Abbreviations: ACEi – Angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, CI-confidence interval, COPD – chronic obstructive pulmonary disease, aSHR- multivariable-adjusted sub-hazard ratio.

**Bold p-value < .05**

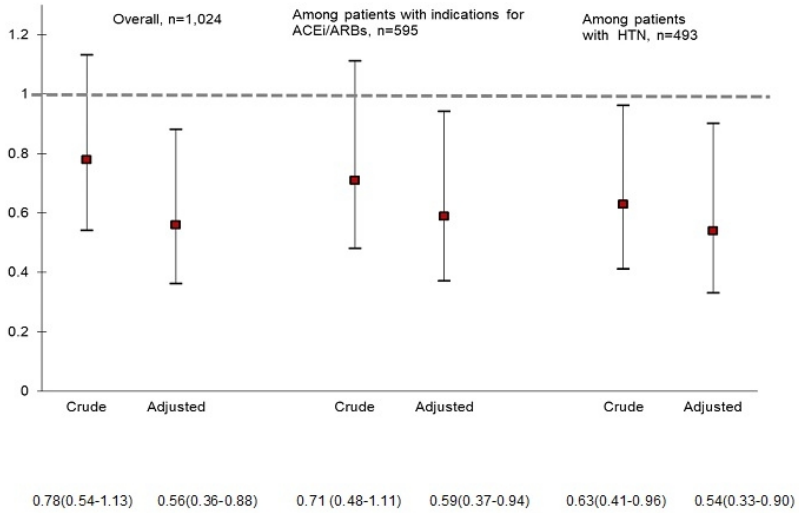


Figure 1. Covid-19 In-Hospital Mortality, Hazard Ratio, 95% Confidence Intervals for ACEi/ARB Use.
Legend. Figure 1 presents crude and adjusted hazards ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

224x153mm (96 x 96 DPI)

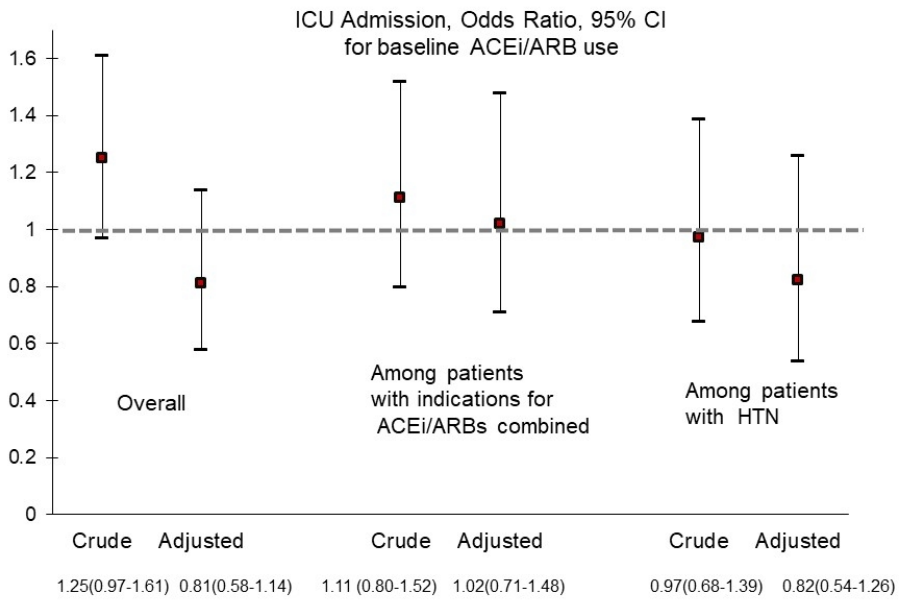


Figure 2. Intensive Care Use, Odds Ratio, 95% CI for ACEi/ARB Use.
Legend: Figure 2 presents crude and adjusted odds ratios and 95% confidence intervals for in-hospital Covid-19 mortality. Indications for ACEi/ARB use included hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant. Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant.

254x190mm (96 x 96 DPI)

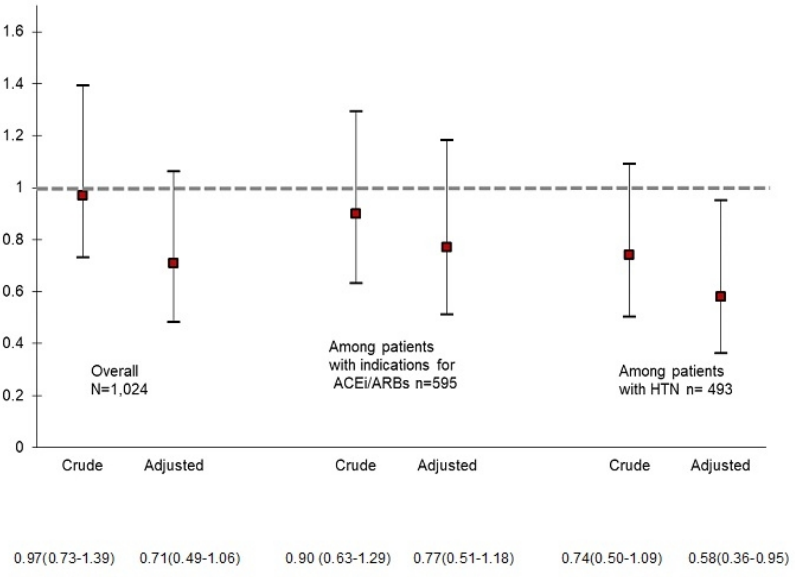


Figure 3. Respiratory Failure, requiring Invasive Mechanical Ventilation, Odd Ratio, 95% Confidence intervals, for ACEi/ARB Use

Legend. Indications for ACEi/ARB use include hypertension, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: hypertension, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020). Among those with hypertension, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs. after July 15, 2020).

222x145mm (96 x 96 DPI)

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.



| | | Reporting Item | Page Number |
|---|---|---|---|
| **Title and abstract** | | | |
| Title | #1a | Indicate the study's design with a commonly used term in the title or the abstract | 2 |

| | | | |
|---|---|---|---|
| Abstract | #1b | Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background / rationale | #2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | #3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | #4 | Present key elements of study design early in the paper | 4 |
| Setting | #5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 |
| Eligibility criteria | #6a | Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. | 4 |
| Eligibility criteria | #6b | For matched studies, give matching criteria and number of exposed and unexposed | n/a |
| Variables | #7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4 |
| Data sources / measurement | #8 | For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than | 5 |

| | | | |
|---|---|---|---|
| | | one group. Give information separately for for exposed and unexposed groups if applicable. | |
| Bias | #9 | Describe any efforts to address potential sources of bias | 5 |
| Study size | #10 | Explain how the study size was arrived at | 4 |
| Quantitative variables | #11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | 5 |
| Statistical methods | #12a | Describe all statistical methods, including those used to control for confounding | 5 |
| Statistical methods | #12b | Describe any methods used to examine subgroups and interactions | 5 |
| Statistical methods | #12c | Explain how missing data were addressed | 5 |
| Statistical methods | #12d | If applicable, explain how loss to follow-up was addressed | n/a |
| Statistical methods | #12e | Describe any sensitivity analyses | n/a |
| **Results** | | | |
| Participants | #13a | Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed | 6 |

| | | | |
|---|---|---|---|
| | | eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable. | |
| Participants | #13b | Give reasons for non-participation at each stage | n/a |
| Participants | #13c | Consider use of a flow diagram | n/a |
| Descriptive data | #14a | Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable. | 6 |
| Descriptive data | #14b | Indicate number of participants with missing data for each variable of interest | 6 |
| Descriptive data | #14c | Summarise follow-up time (eg, average and total amount) | 7 |
| Outcome data | #15 | Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable. | 7 |

| | | | |
|---|---|---|---|
| Main results | #16a | Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 7,8 |
| Main results | #16b | Report category boundaries when continuous variables were categorized | 6 |
| Main results | #16c | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| n/a | | | |
| Other analyses | #17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 7,8 |
| **Discussion** | | | |
| Key results | #18 | Summarise key results with reference to study objectives | 8 |
| Limitations | #19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. | 9 |
| Interpretation | #20 | Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. | 9 |
| Generalisability | #21 | Discuss the generalisability (external validity) of the study results | 10 |
| **Other Information** | | | |

| | | | |
|---|---|---|---|
| Funding | #22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 11 |